



VCU

Stravitz-Sanyal Institute for
Liver Disease and Metabolic Health
School of Medicine



UPDATES IN ALCOHOL-ASSOCIATED LIVER DISEASE

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Commercial or Non-Profit Interest	Relationship
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Echosens, Madrigal, Novo-Nordisk.	Research Support, Educational Support

AIM FOR THIS TALK

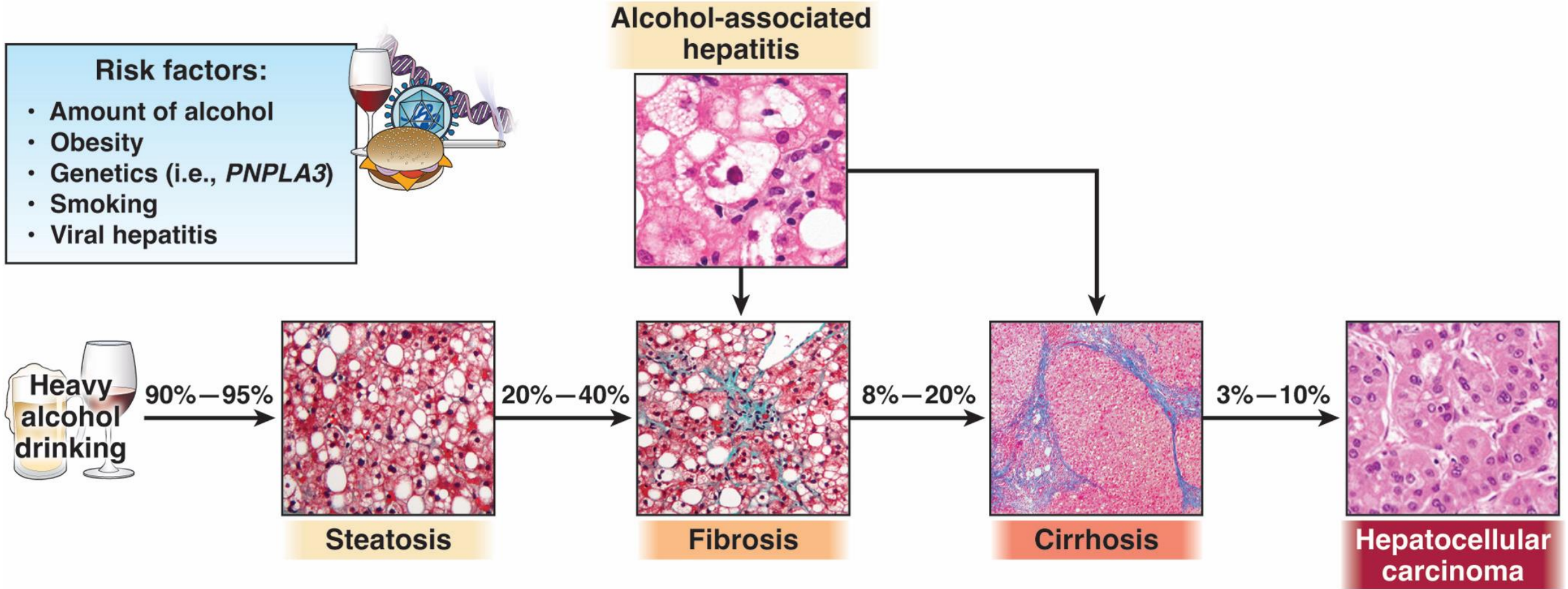
1. Epidemiology of alcohol-associated liver disease (ALD)
2. Alcohol-associated hepatitis (AH)
3. MetALD
4. Alcohol use disorder (AUD) in the context of ALD
5. Public Health



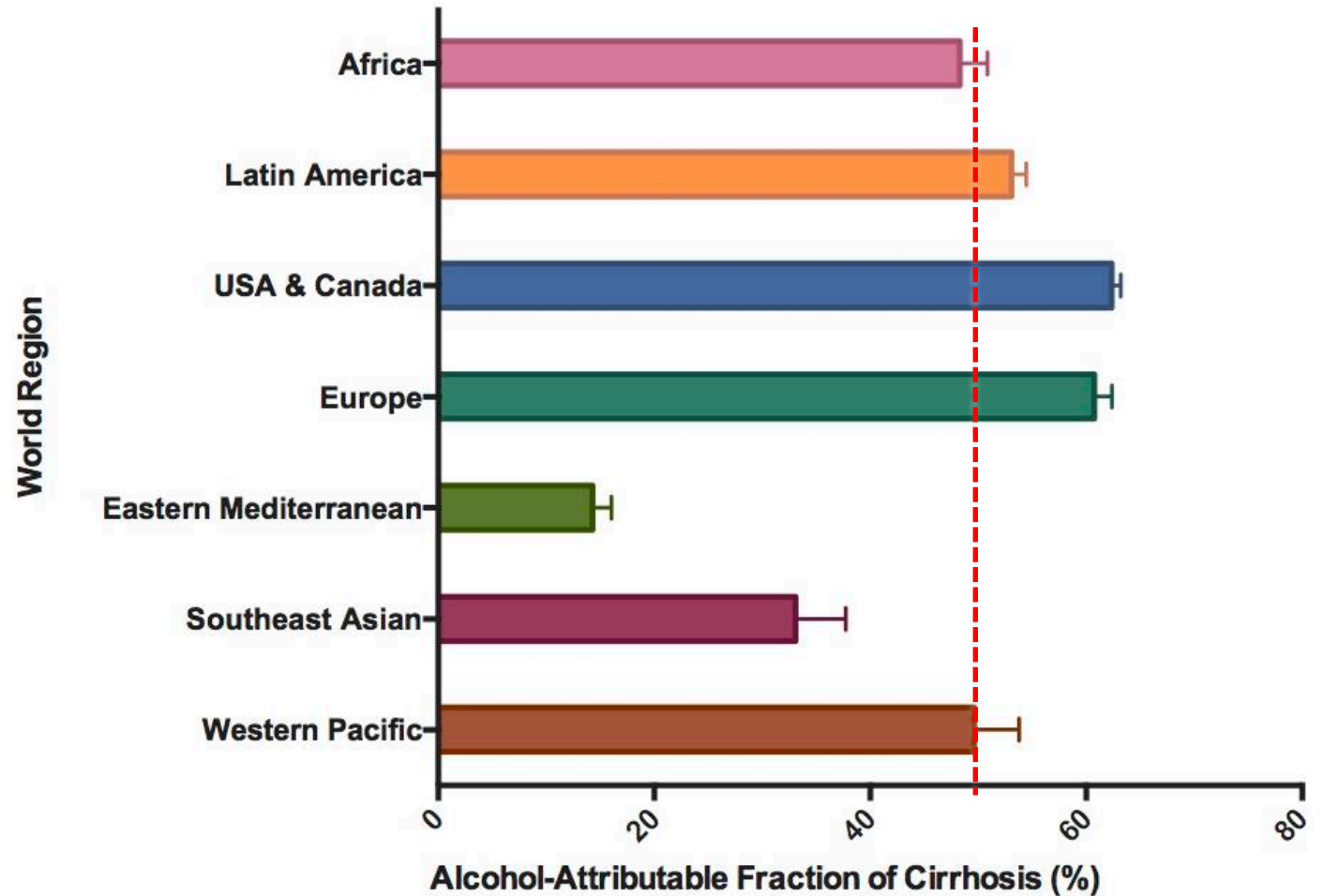
Image from: photos.com

Epidemiology of alcohol-associated liver disease (ALD)

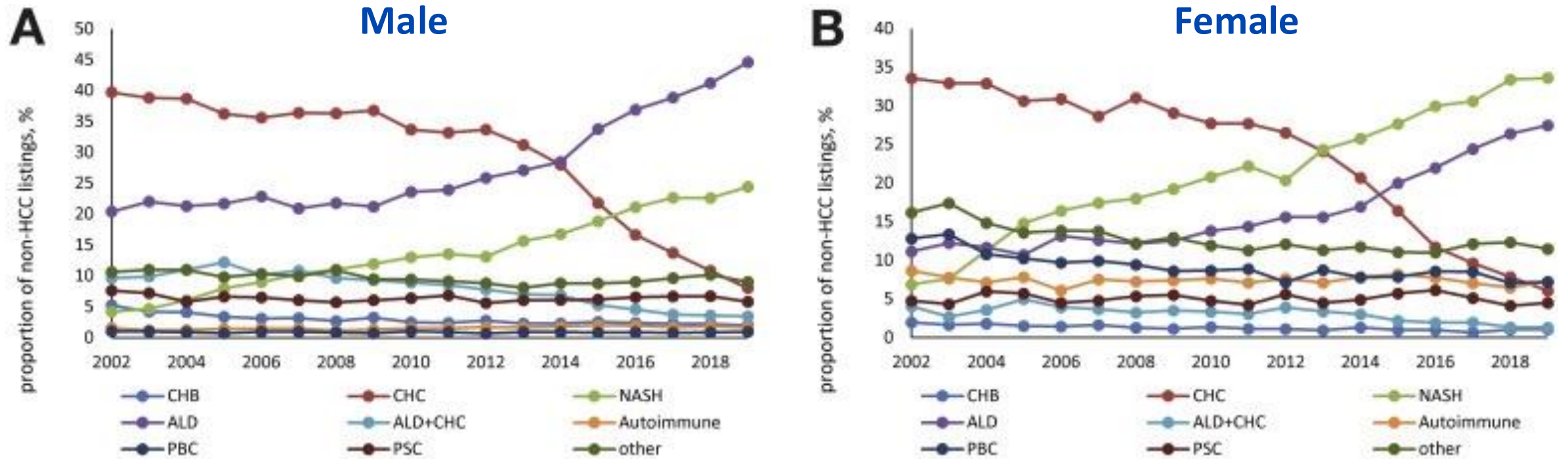
NATURAL HISTORY



Alcohol represents **more than 50%** of the attributable fraction of **cirrhosis** in America and Europe.



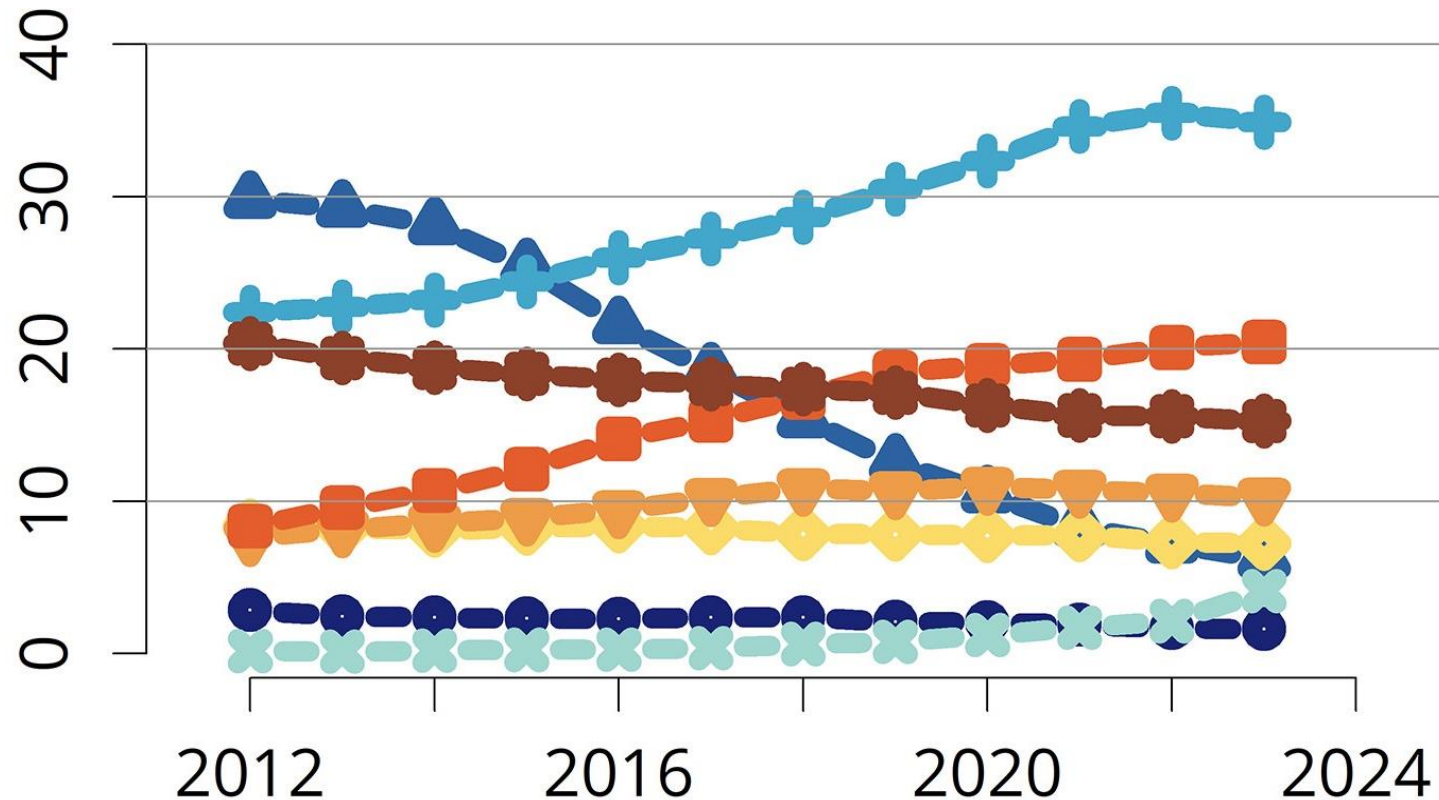
ALD related trends on liver transplantation



Liver Transplant for AH > HCV in the US

OPTN/SRTR 2023 Annual Data Report

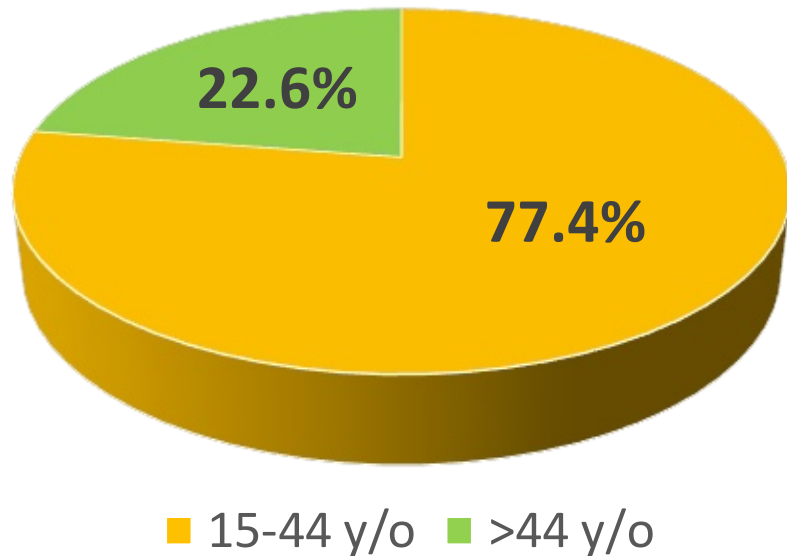
- ALD is the leading indication for LT



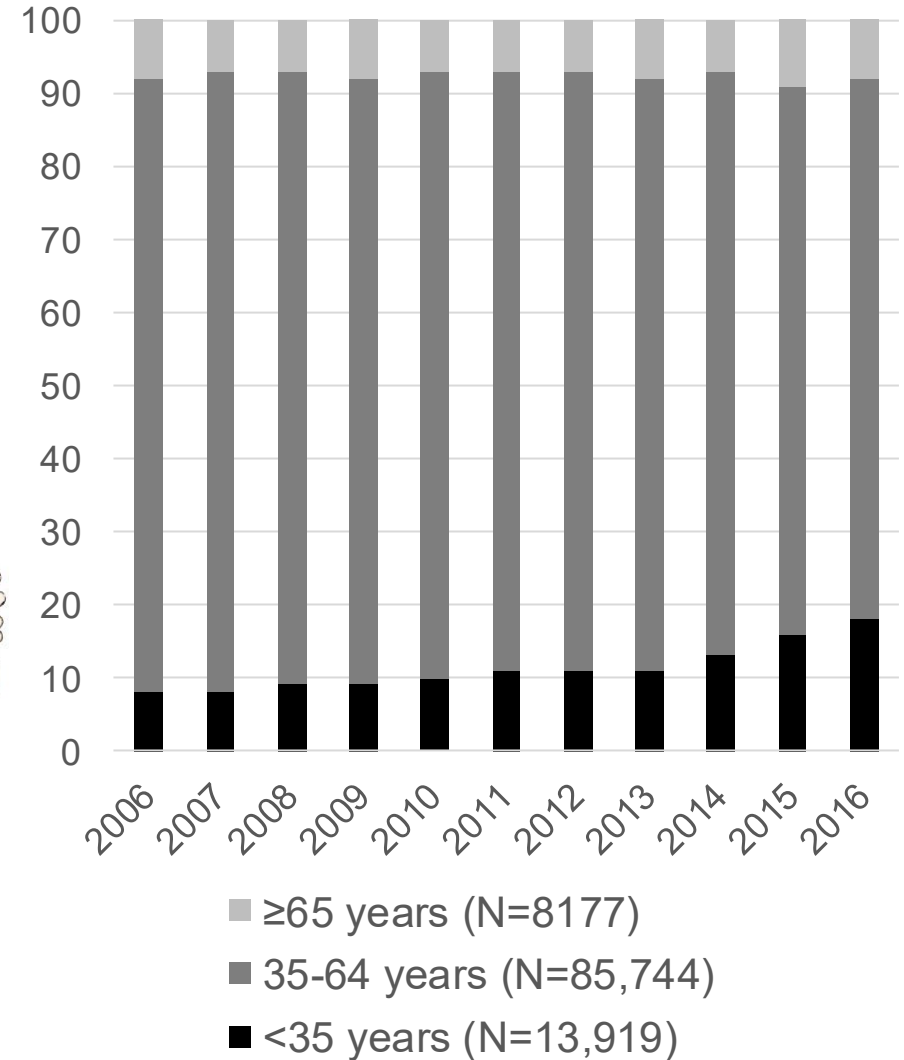
Primary Diagnosis	Value
ALD	41.1%
AC	34.6%
AH	6.5%
MASH	20.3%
HCC	10.4%
Cholestatic	7.4%
HCV	4.2%

New high-risk groups

There is an increasing incidence of AH in **young people and women**.

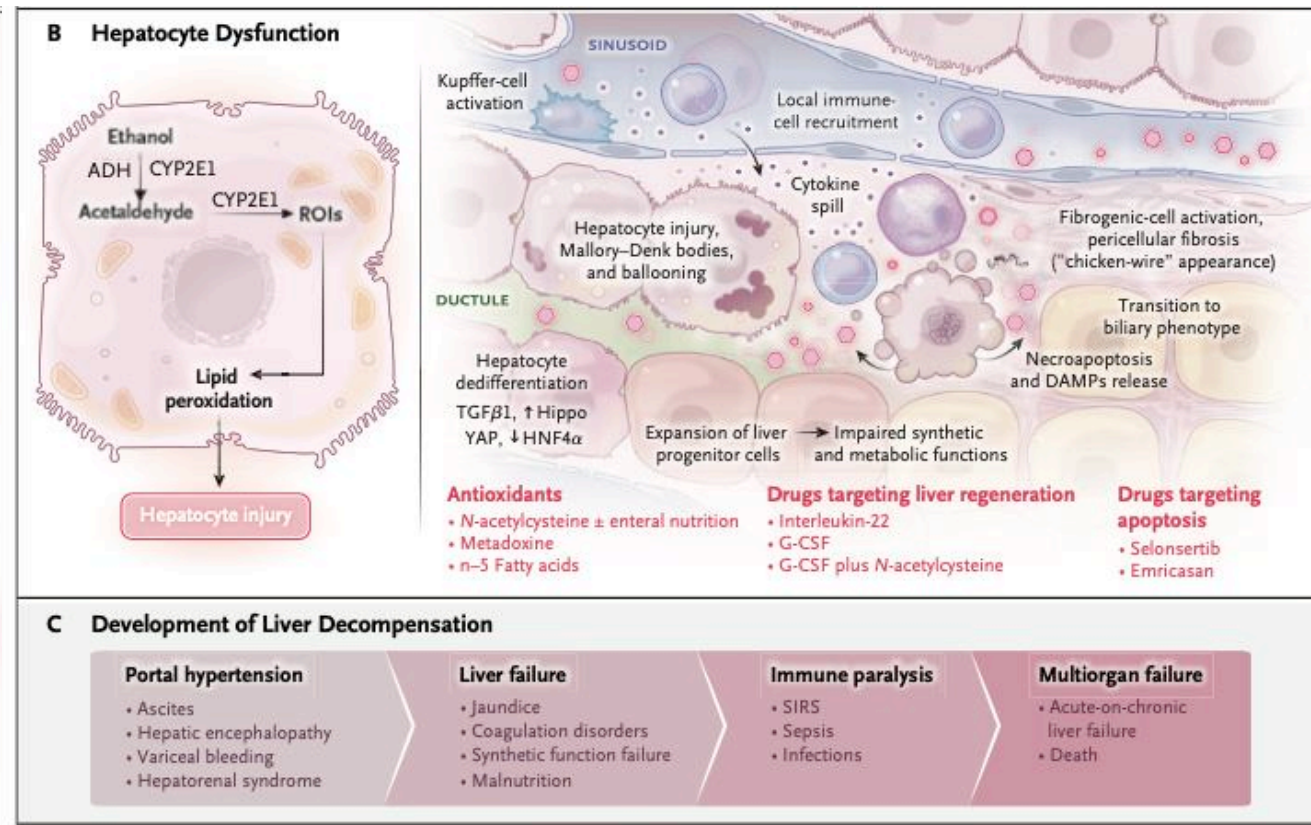
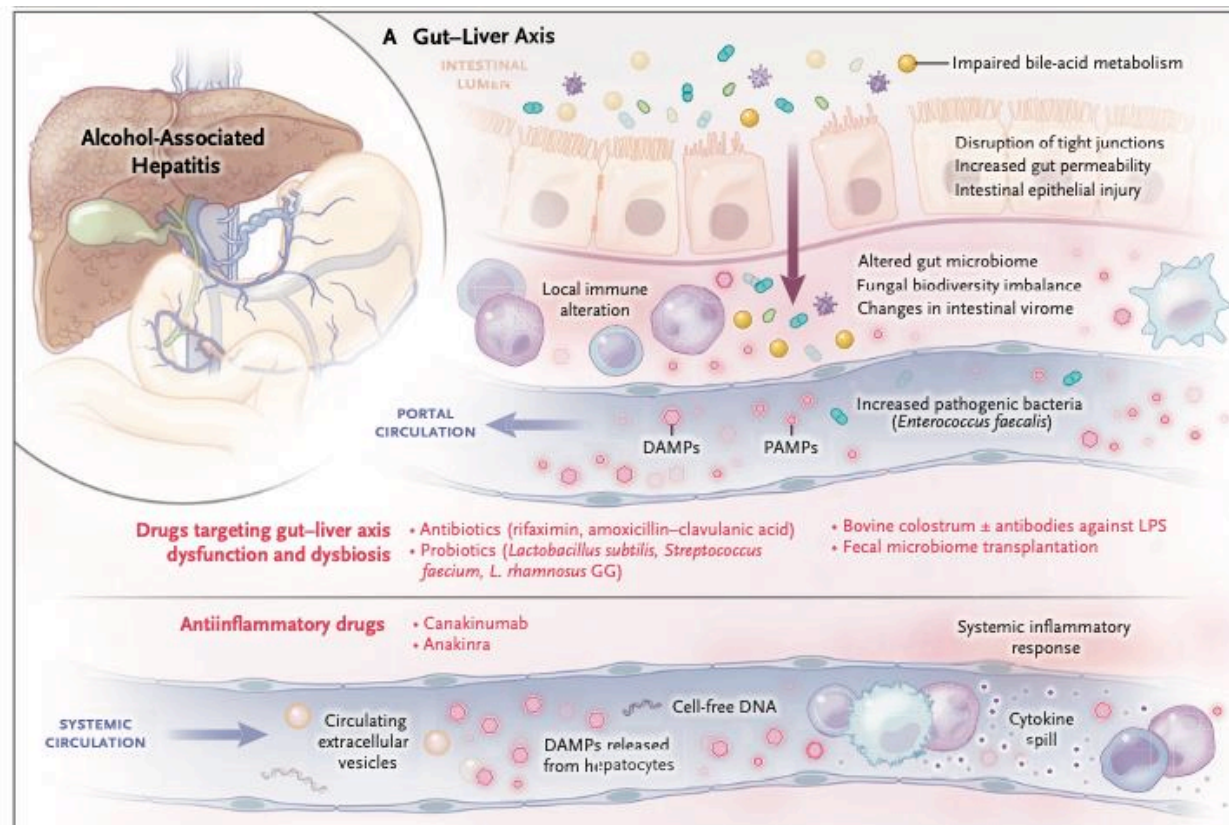


AH trends in the US

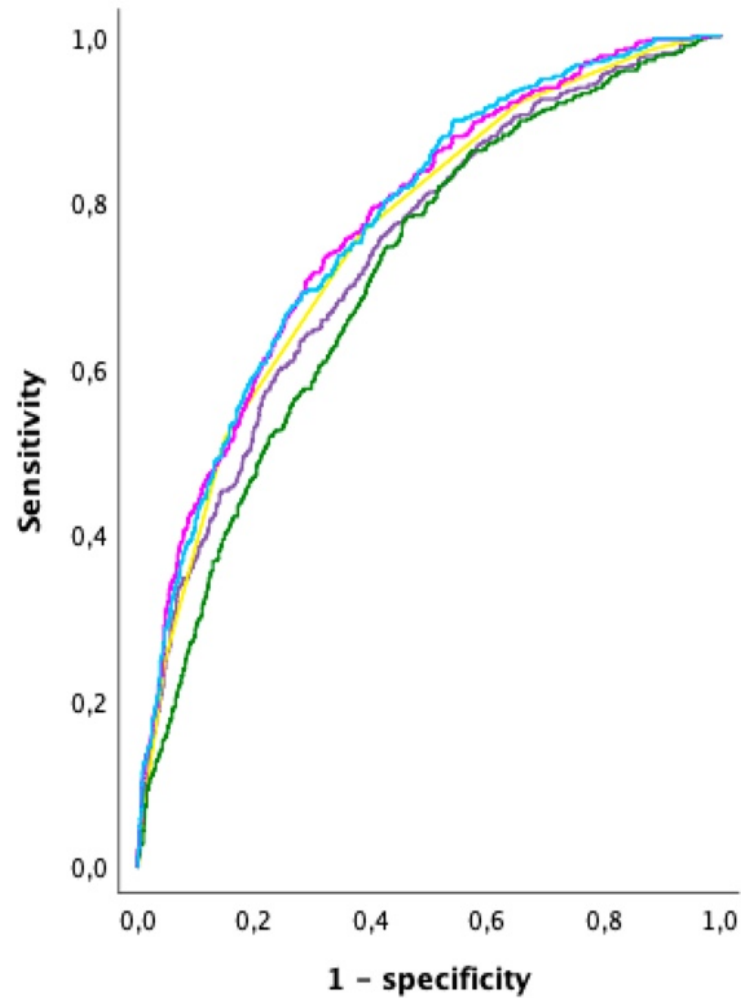


Alcohol-associated hepatitis (AH)

Alcohol-associated Hepatitis (AH)



Prognosis assessment / indication for treatment



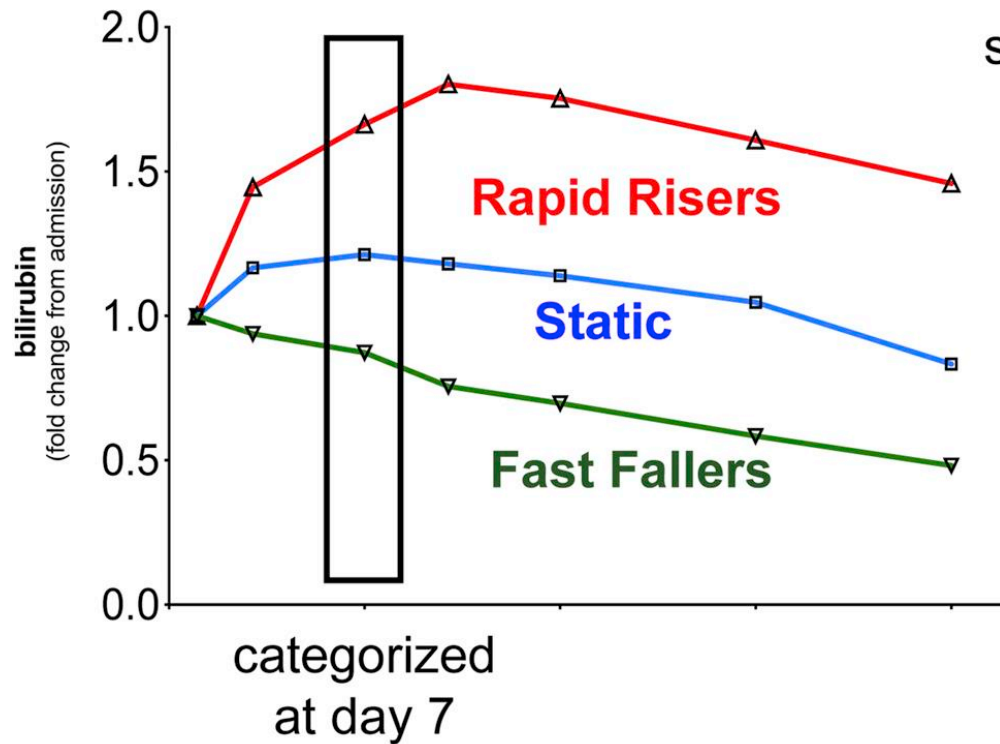
— ABIC
— GHAS
— mDF
— MELD-Na
— MELD

	AUC	p	CI 95%
MELD	0.773	<0.001	0.750-0.795
MELD-Na	0.773	<0.001	0.750-0.795
mDF	0.709	<0.001	0.684-0.734
GHAS	0.756	<0.001	0.733-0.780
ABIC	0.737	<0.001	0.713-0.762

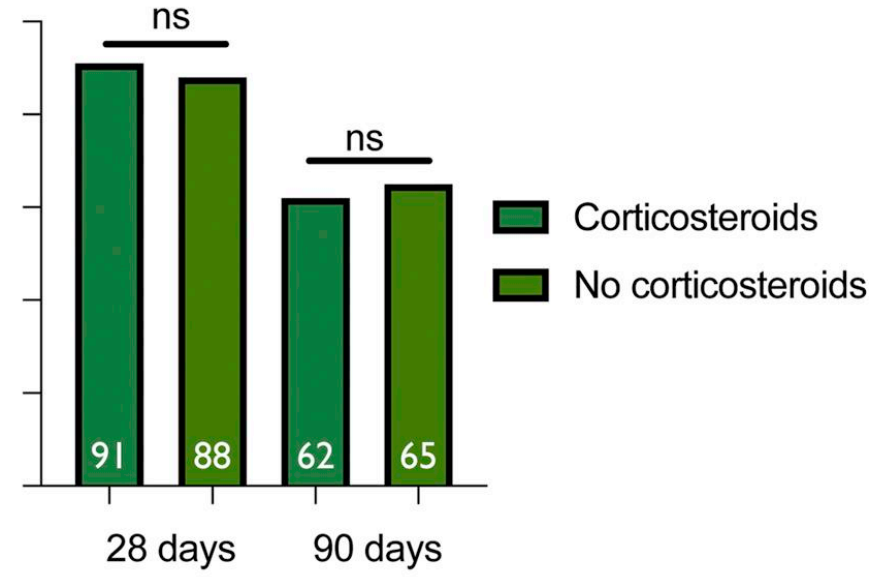
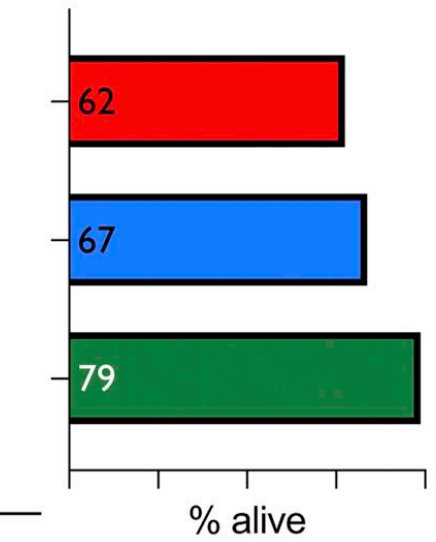
	MELD	MELD-Na	mDF	GHAS	ABIC
MELD	-	0.930	<0.001	0.092	0.009
MELD-Na		-	<0.001	0.142	0.018
mDF			-	<0.001	0.004
GHAS				-	0.142
ABIC					-

Prognosis assessment

Trajectories of bilirubin in alcoholic hepatitis



Fast Fallers:
more likely to survive at 90 days
do not benefit from corticosteroids, even in severe disease



Clinical Gastroenterology and Hepatology

TREATMENT

Is there a therapeutic window of MELD for the use of corticosteroids?



We validated the use of steroids in severe alcohol-related hepatitis (MELD score >20)



Corticosteroids decreased mortality at 30 days (HR=0.59)



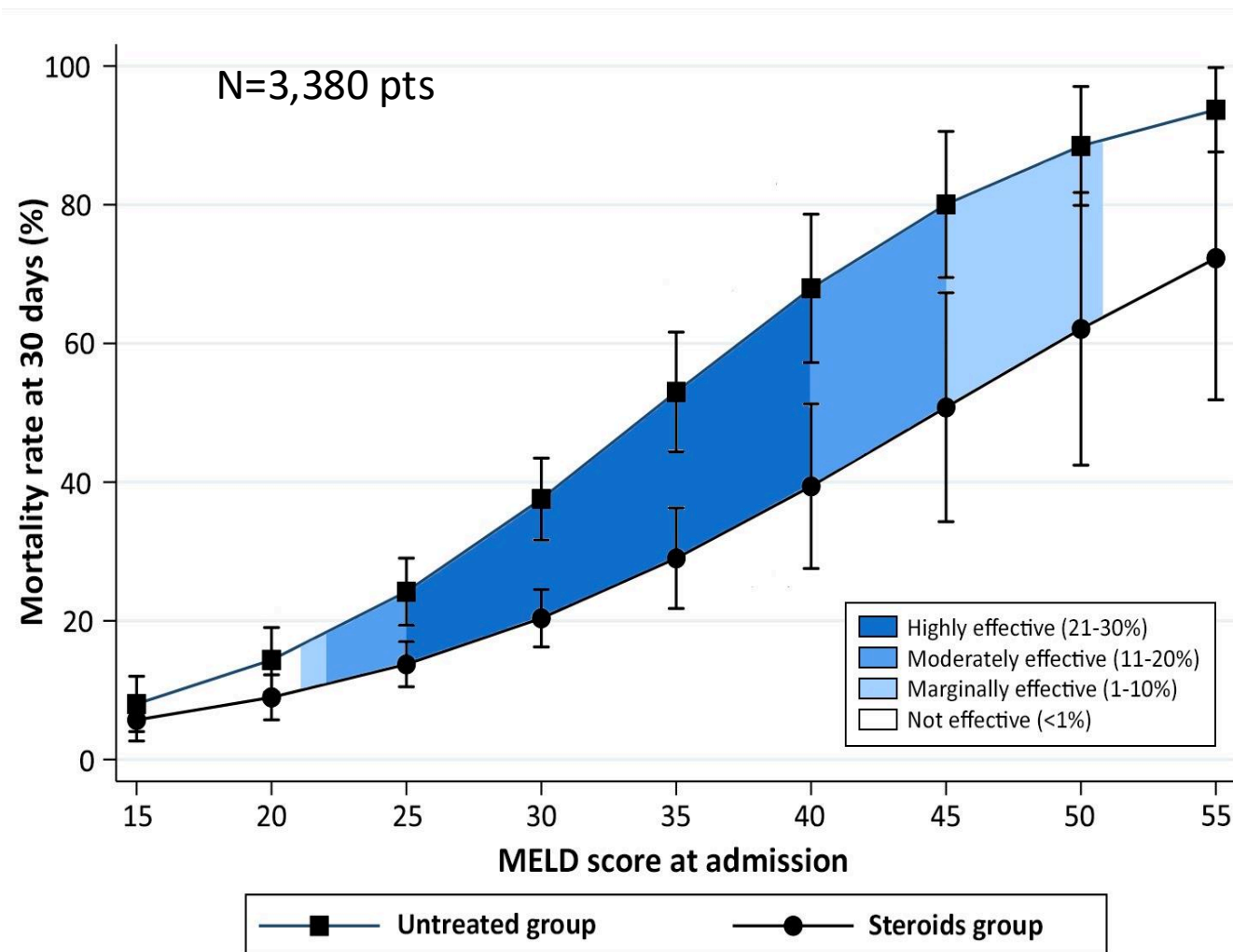
The most significant benefit was MELD range 25-39



Futility of treatment could not be demonstrated in this study



Survival benefit was not sustained at 90 or 180 days

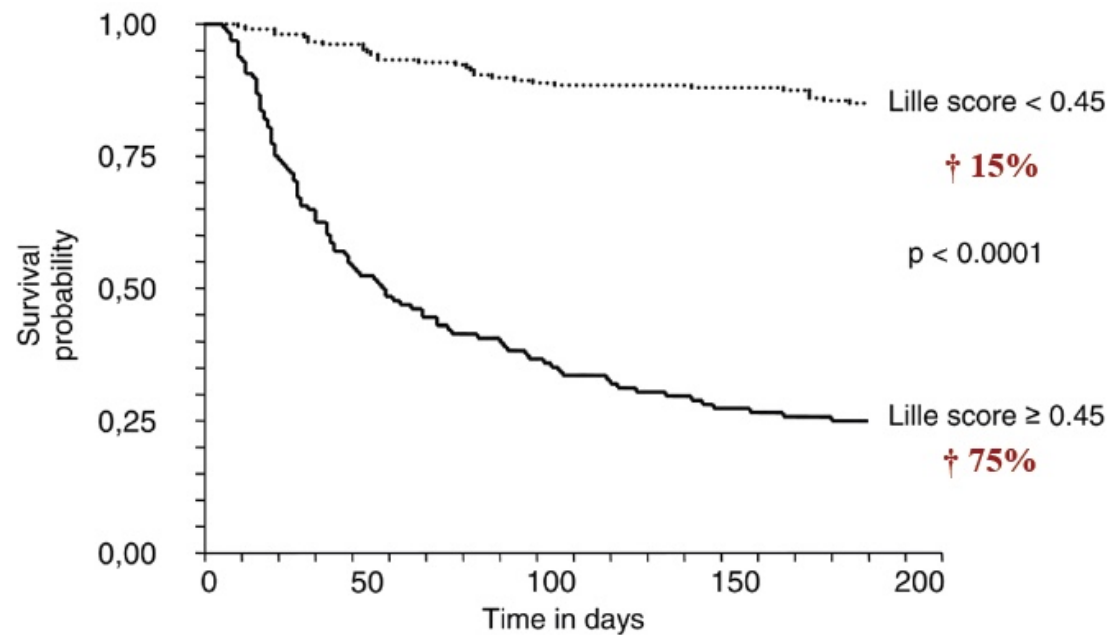


Treatment – Specific Treatment - CORTICOSTEROIDS

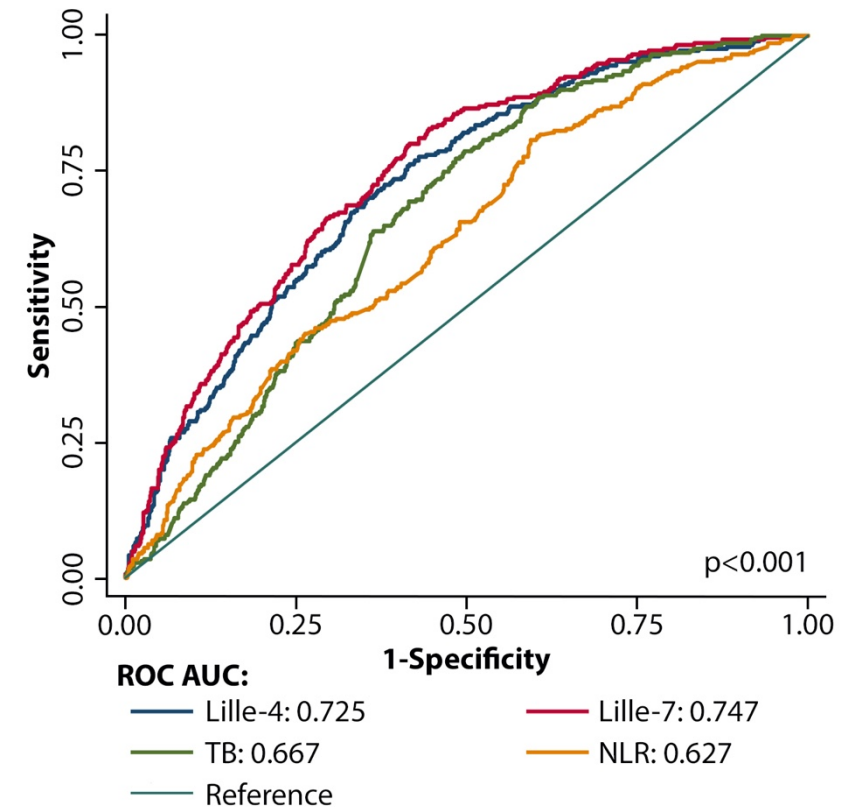
Evaluation of the response to corticosteroids.

Lille score: 40% NO response to corticosteroids.

N = 418 patients in 5 clinical trials

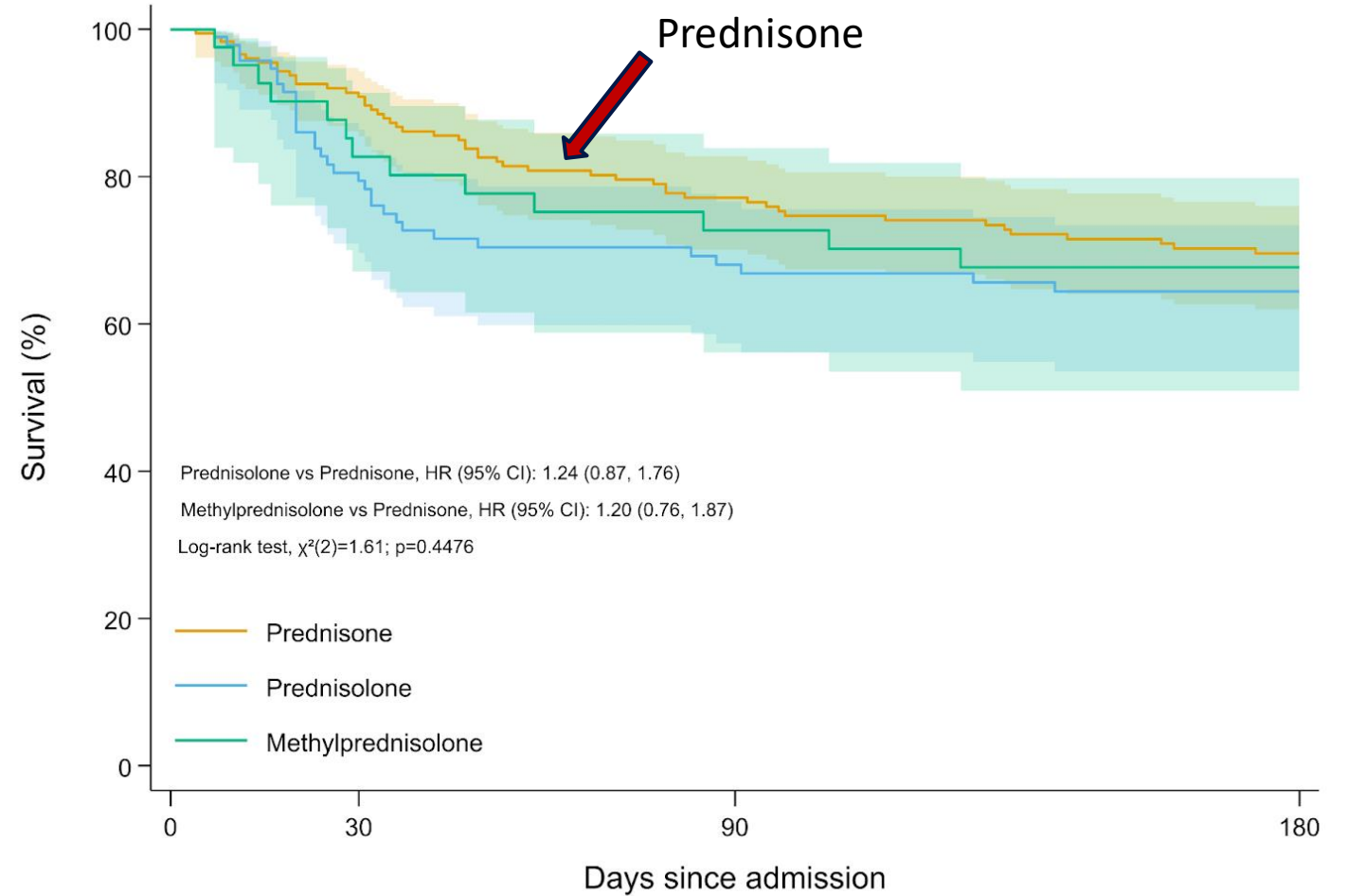


Comparison of models to predict response in patients with AH undergoing corticosteroid treatment (30-day mortality)



What about the type of corticosteroids?

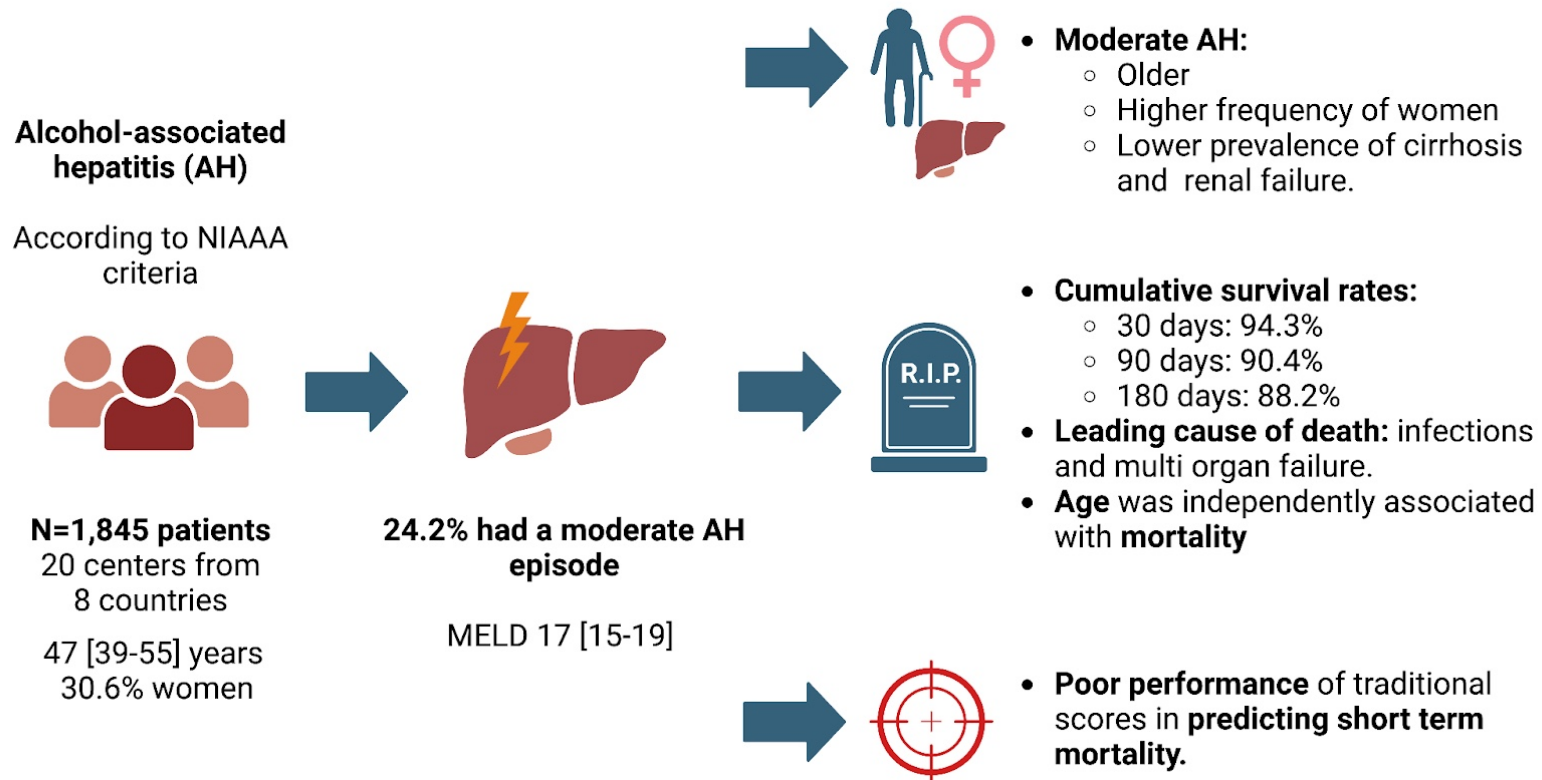
- **A total of 324 patients with severe AH**
- **No Significant Differences in 30-Day Mortality between Prednisolone, Prednisone, or Methylprednisolone**
- **Survival Rates at 30 days post-admission:**
 - Prednisone: 90.8% (85.5–94.3%)
 - Prednisolone: 79.4% (69.7– 86.4%)
 - Methylprednisolone: 82.7% (67.1– 91.4%)
- **Therapeutic Flexibility** in the choice of corticosteroid may be possible without compromising short-term survival



Number at risk				
	0	30	90	180
Prednisone	186	156	125	107
Prednisolone	95	73	58	52
Methylprednisolone	43	33	29	27

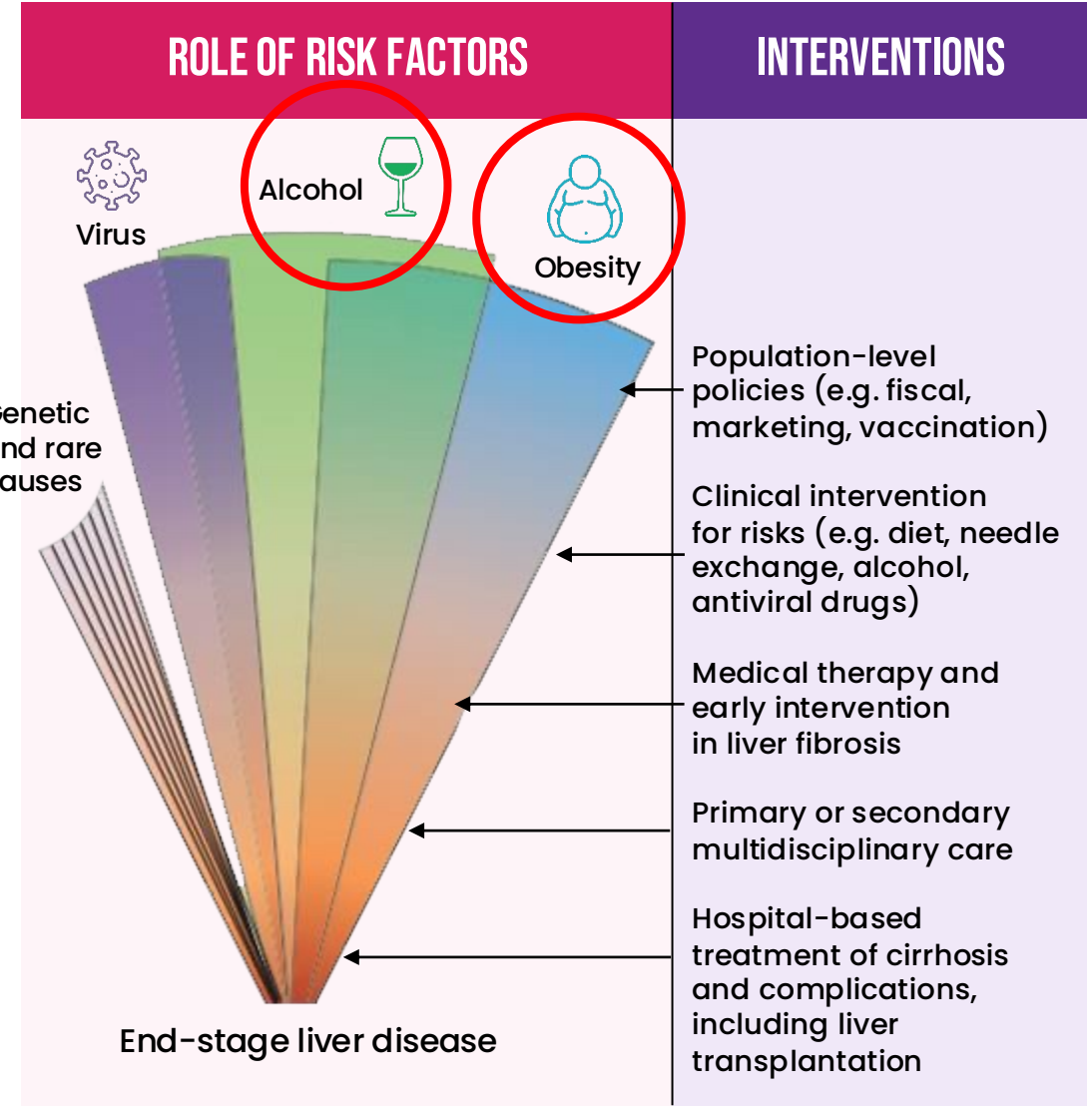
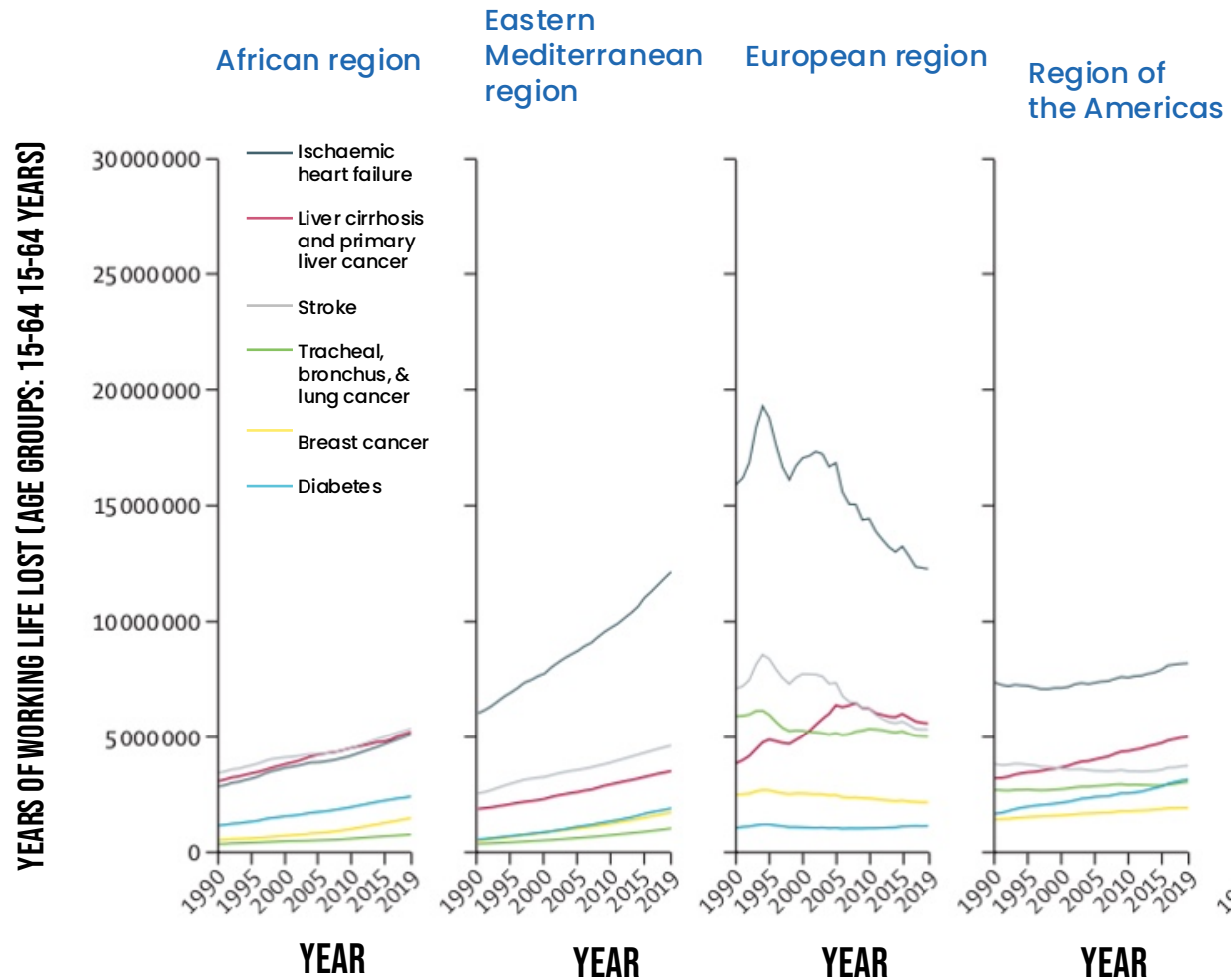
What about the “moderate/non-severe” AH?

MODERATE ALCOHOL-ASSOCIATED HEPATITIS: A REAL-WORLD MULTICENTER STUDY

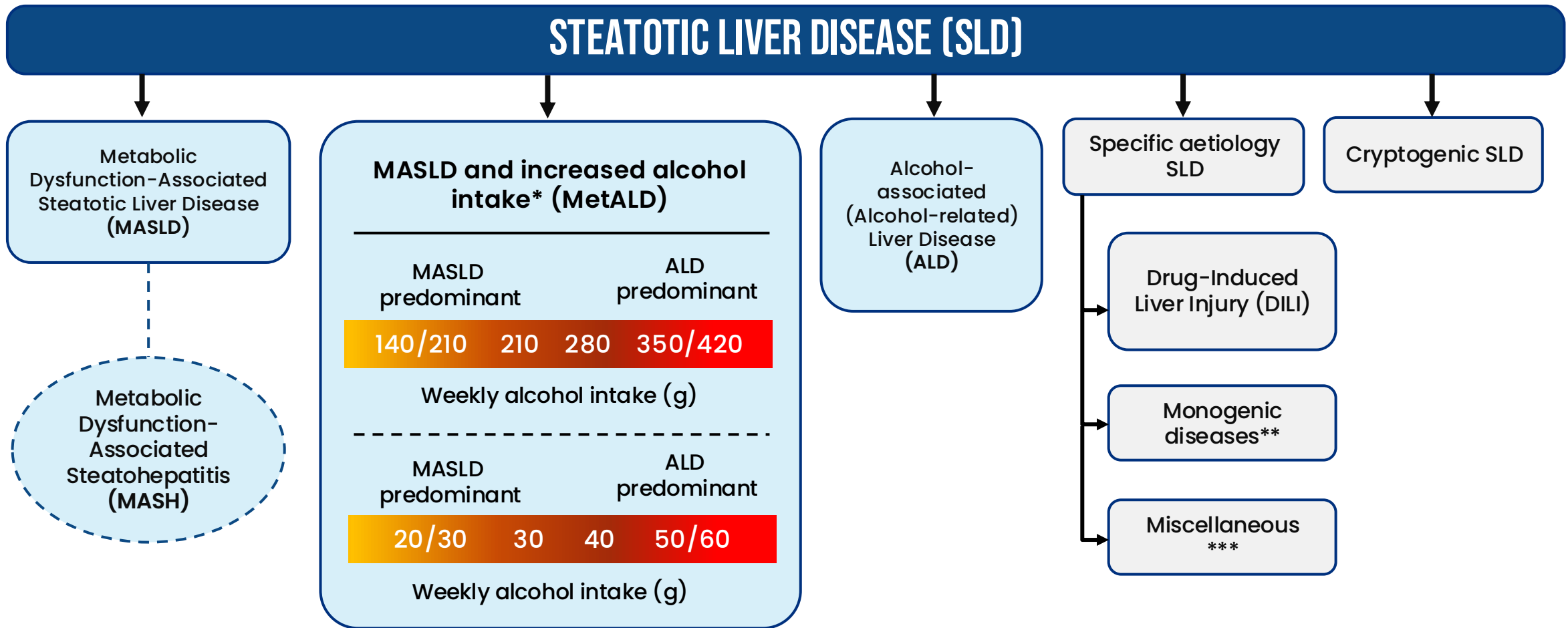


MetALD

Potential years of working life lost, and leading causes by WHO region



NEW NOMENCLATURE: STEATOTIC LIVER DISEASE



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

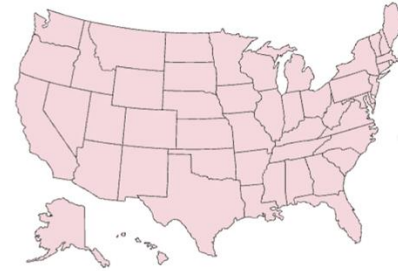
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Epidemiology

Prevalence of Steatotic Liver Disease in the US: NHANES 2017-2020

Background and Aims: Following a Delphi consensus process, the term "steatotic liver disease" (SLD) was introduced to replace "fatty liver disease". Using the NHANES dataset from 2017-2020 we aimed to unveil the prevalence of SLD and its sub-categories in the US.



SLD

37.87%
(95% C.I: 35.1%-40.7%)

MASLD

32.45%
(95%C.I: 29.8%-35.2%)



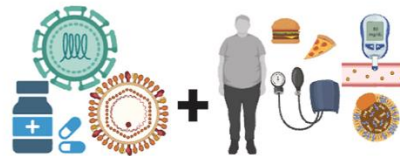
MetALD

2.56%
(95%C.I: 1.91%-3.41%)



Other Combination Aetiology

1.14%
(95%C.I: 0.88%-1.49%)



ALD

1.17%
(95%C.I: 0.71%-1.92%)



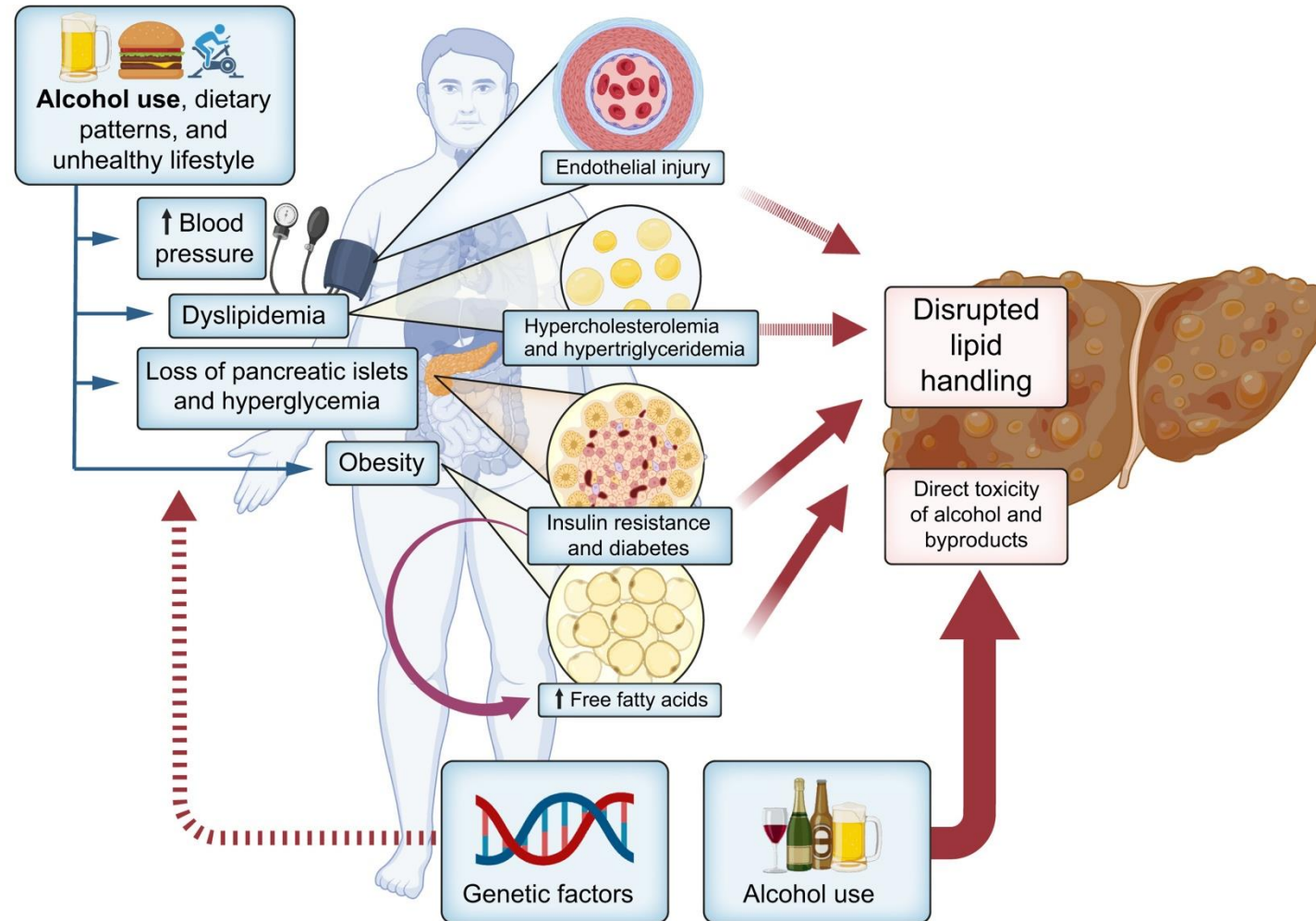
Cryptogenic/ Other

0.32%
(95%C.I: 0.17%-0.61%)



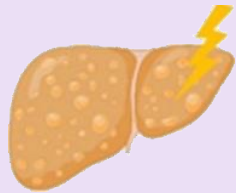
Clinical Gastroenterology
and Hepatology

Interplay Between Metabolic Dysfunction and Alcohol



DETECTION OF ALCOHOL MISUSE IN MASLD

FATTY LIVER DISEASE



Steatosis



Alcohol



Steatohepatitis



Obesity



T2DM



Diet



Cirrhosis

METHODS



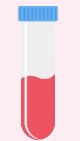
Questionnaire



Sample collection



AUDIT-C



MCV
GGT
CDT
ANI



uEtG



hEtG
FAEE

SCR for alcohol consumption
+ metabolic characterization

RESULTS & CONCLUSIONS

Moderate to excessive alcohol consumption in



28.6% of NAFLD patients
25.0% of MAFLD patients

Optimal diagnostic means

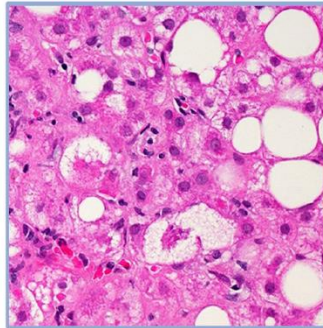


hEtG: AUC 0.927
+ uEtG: AUC 0.754
+ AUDIT-C: AUC 0.733

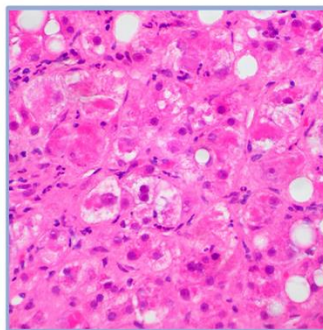
The alcohol-attributable risk of steatotic liver disease

MetALD

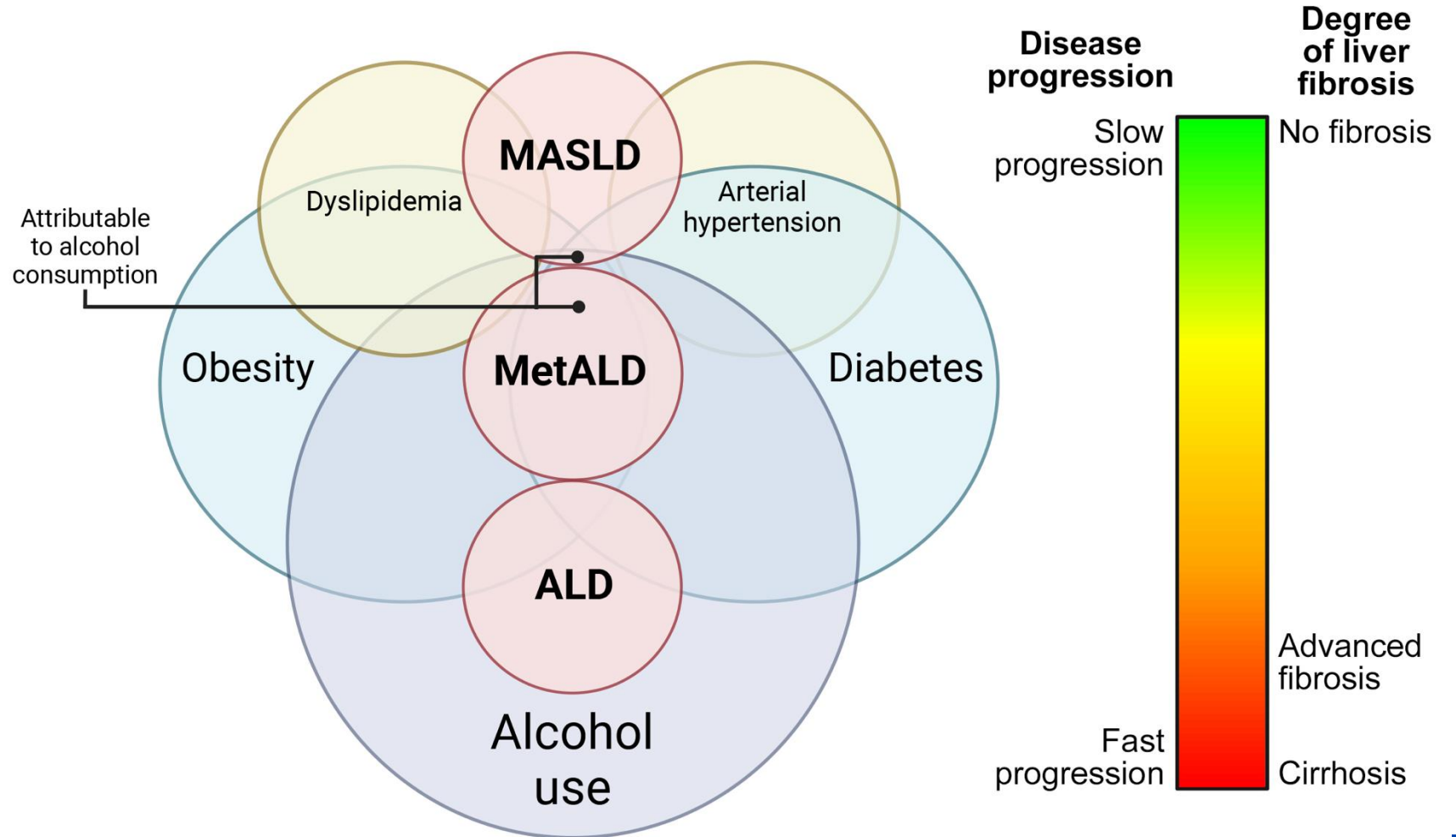
Histological features



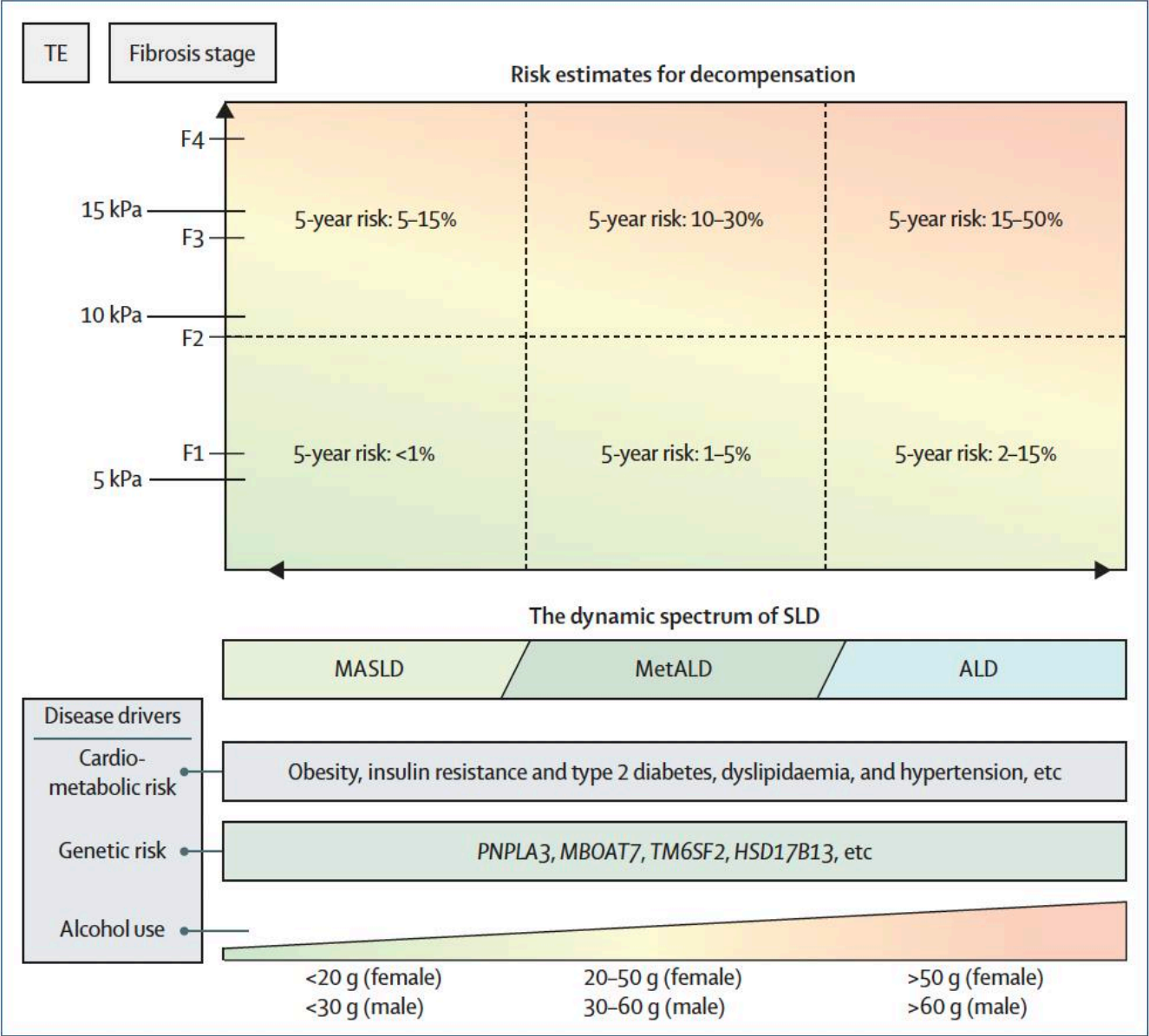
Non-specific steatotic liver disease features



Specific alcohol-related liver disease features

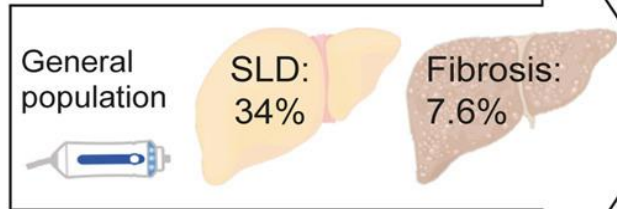


Drivers of Liver Disease

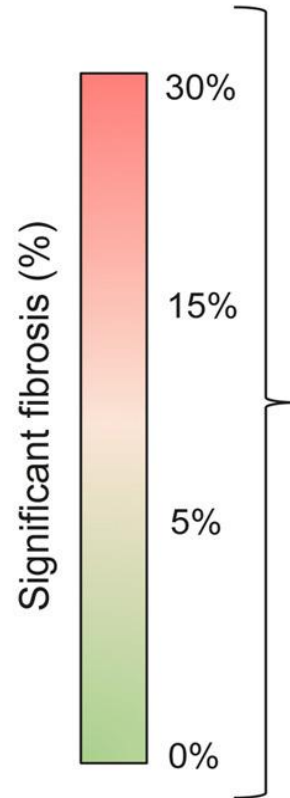


Role of Cardiometabolic Risk Factors

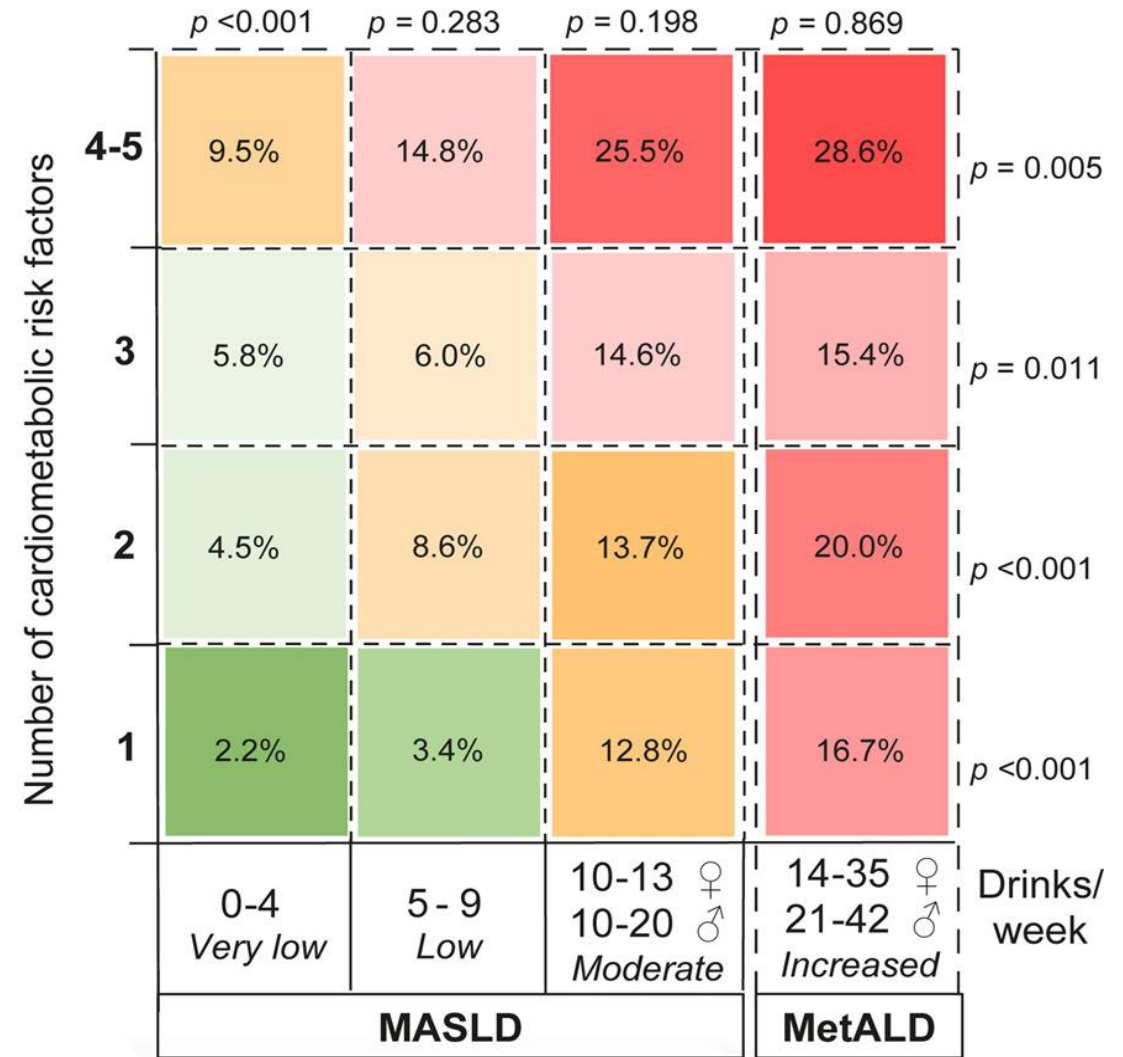
Derivation sample: Spain,
ETHON cohort (n = 6,826)



Validation sample: U.S.,
NHANES cohort (n = 4,427)

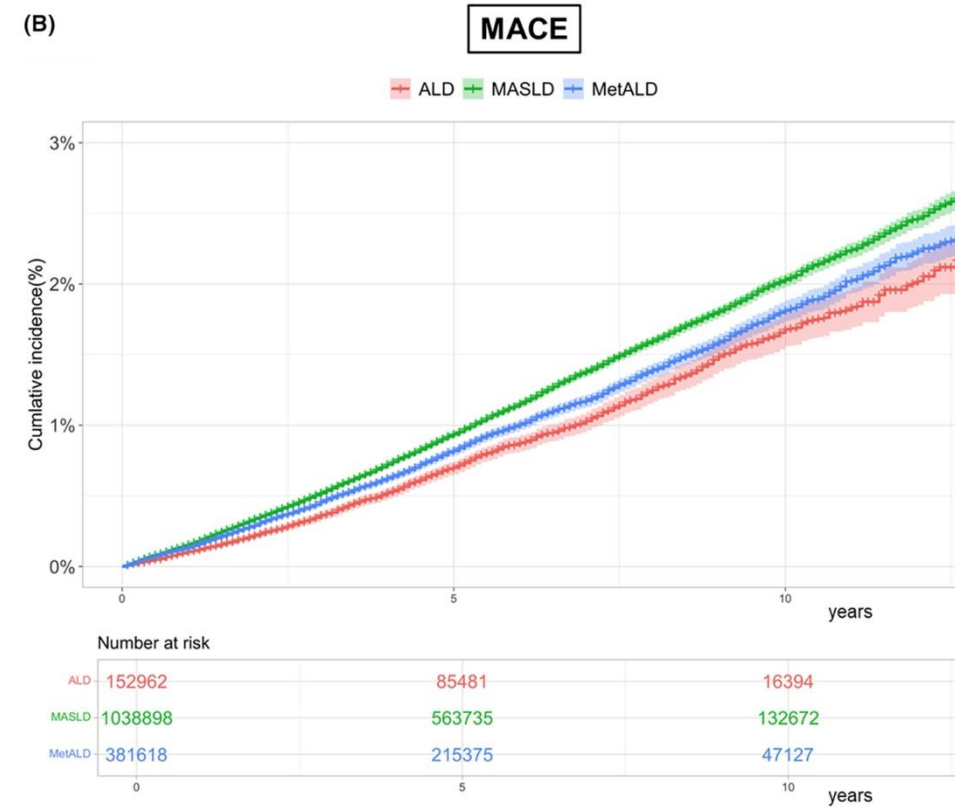
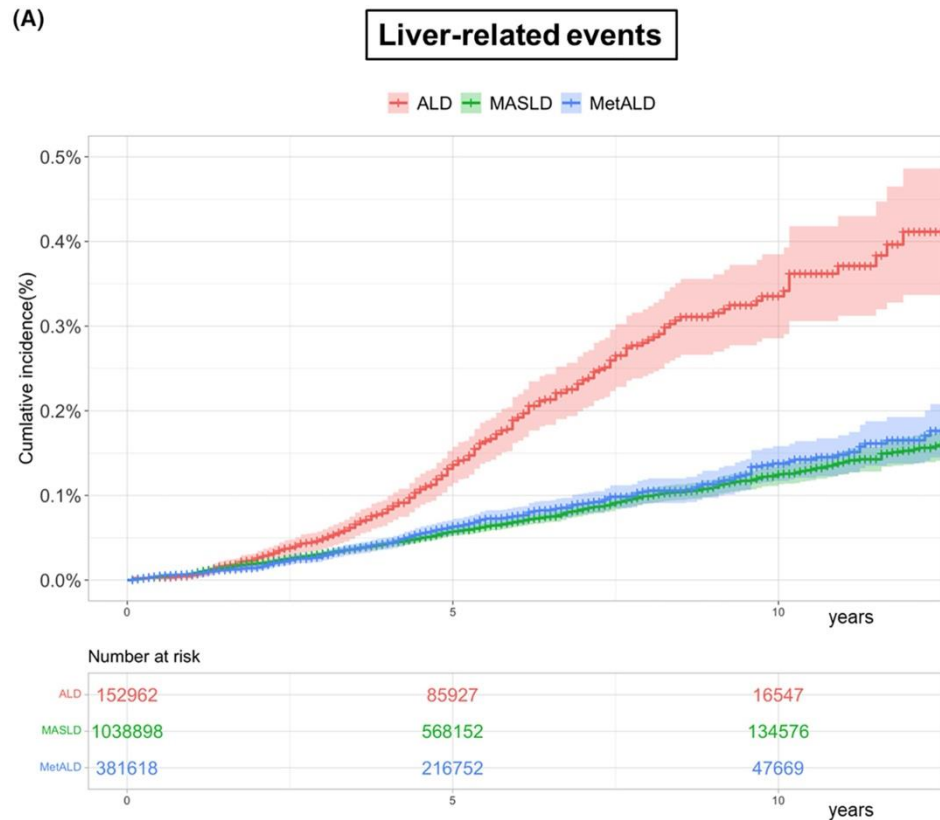


- Steatotic liver disease was defined as CAP ≥ 275 dB/m
- Significant fibrosis was defined as LSM ≥ 8.0 kPa
- Results refers to the derivation cohort
- Analysis was performed with Chi² test



Liver-related events and MACEs in SLD

761,400 Japanese patients diagnosed with MASLD, MetALD or ALD

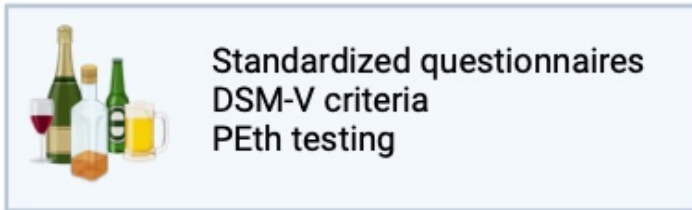


PEth: Improving identification of MetALD subtype

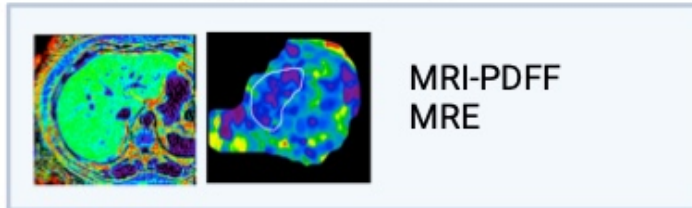
Study cohort: San Diego Liver Study



Alcohol use assessment

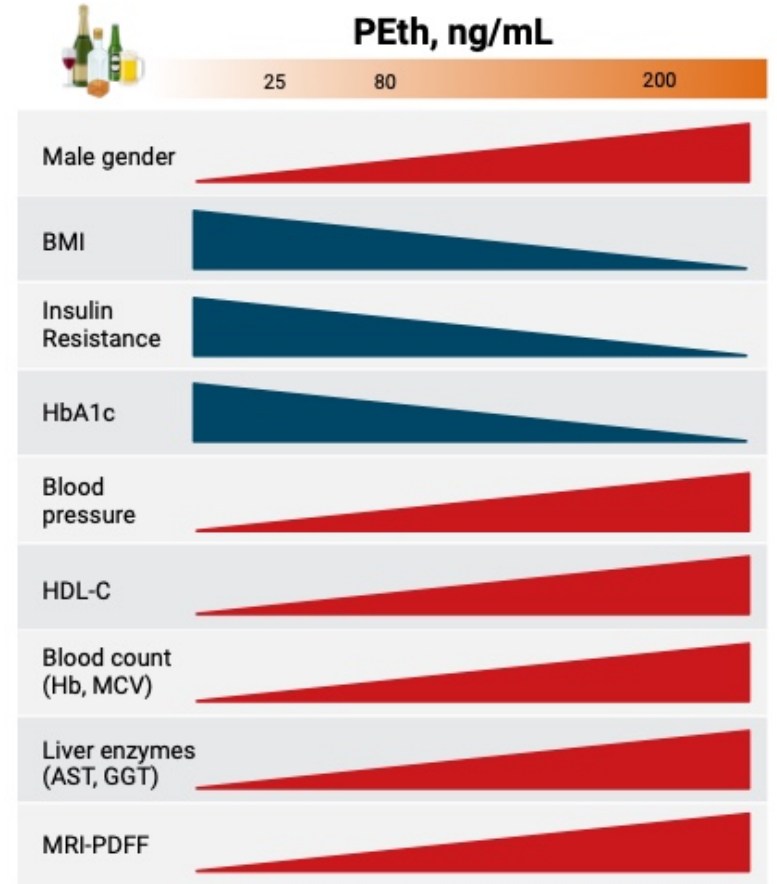
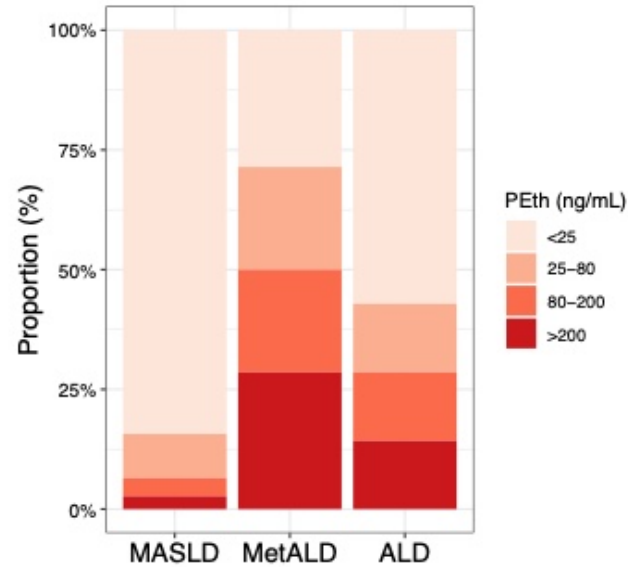


Liver disease phenotyping

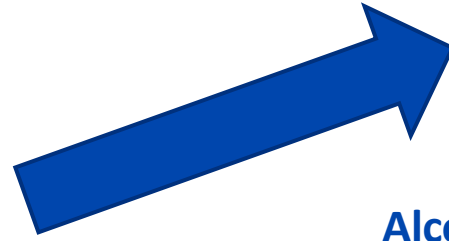
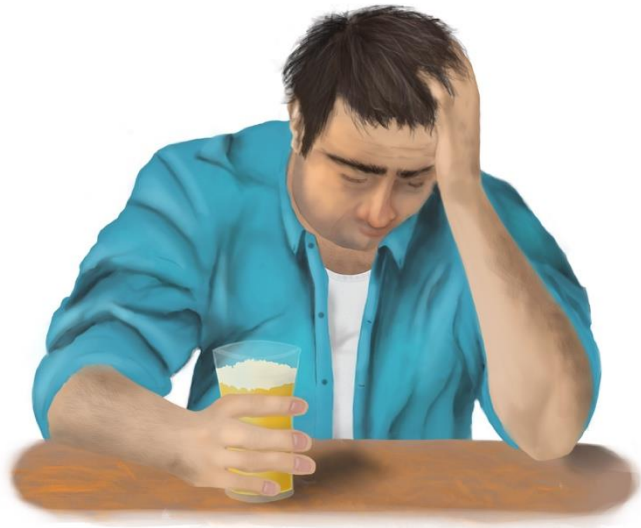


PEth + Self-reported alcohol use

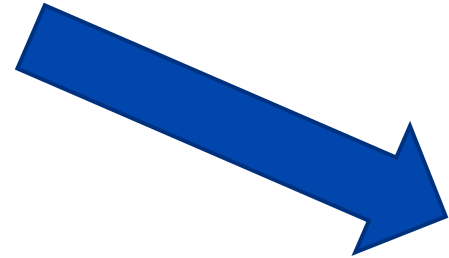
16% underreported alcohol use in SLD
↑ 4-fold increase in MetALD diagnoses
↑ 3-fold increase in ALD diagnoses



Alcohol use disorder (AUD) in the context of ALD



Alcohol-associated liver disease (ALD)



Alcohol use disorder (AUD)

PHARMACOLOGICAL THERAPY FOR ABSTINENCE

Proven to be safe and efficient in ALD

Baclofen (10 mg TID; 80 mg QD max)

Probably safe but not proven in ALD patients

Acamprosate (666 mg TID)

Naltrexone (PO: 50 mg QD IM: 380 mg monthly)

Nalmefene (Max daily dose: 1 tablet 18 mg)

Topiramate (300 mg QD)

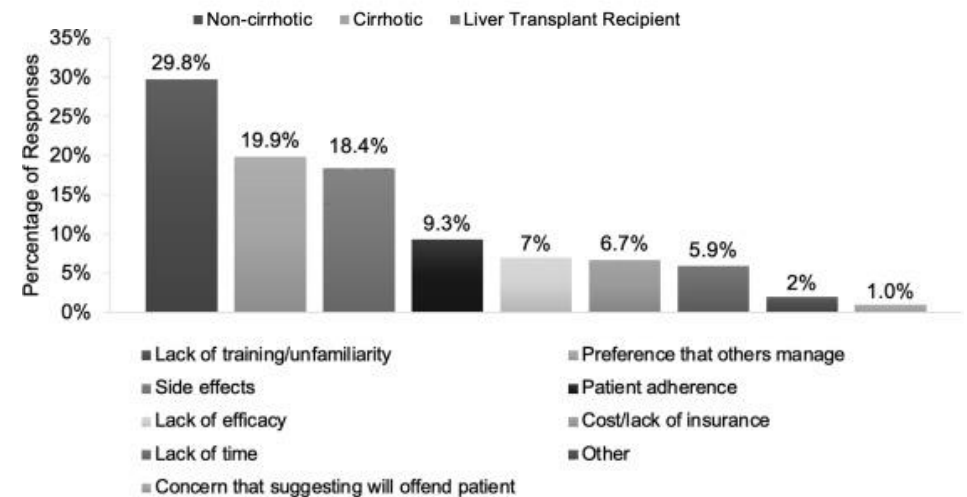
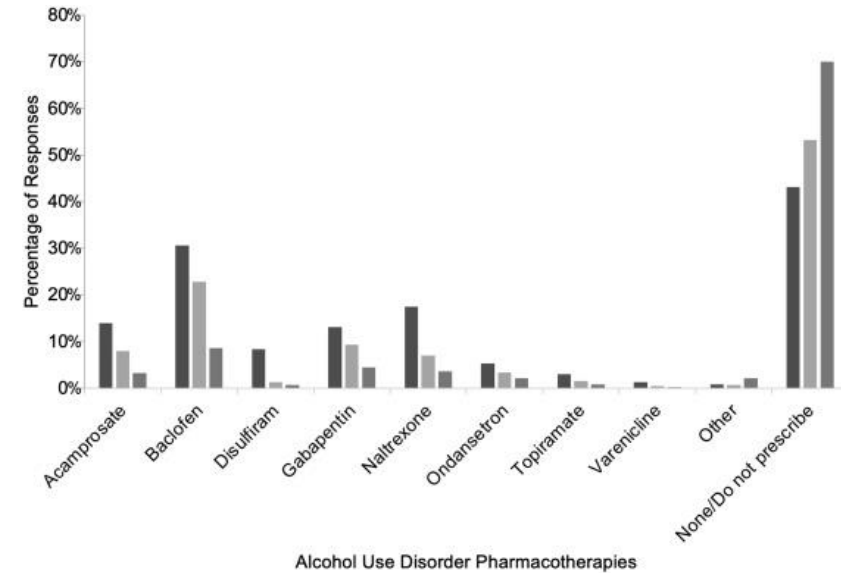
Gabapentin (900-1800 mg QD)

Varenicline (2 mg QD)

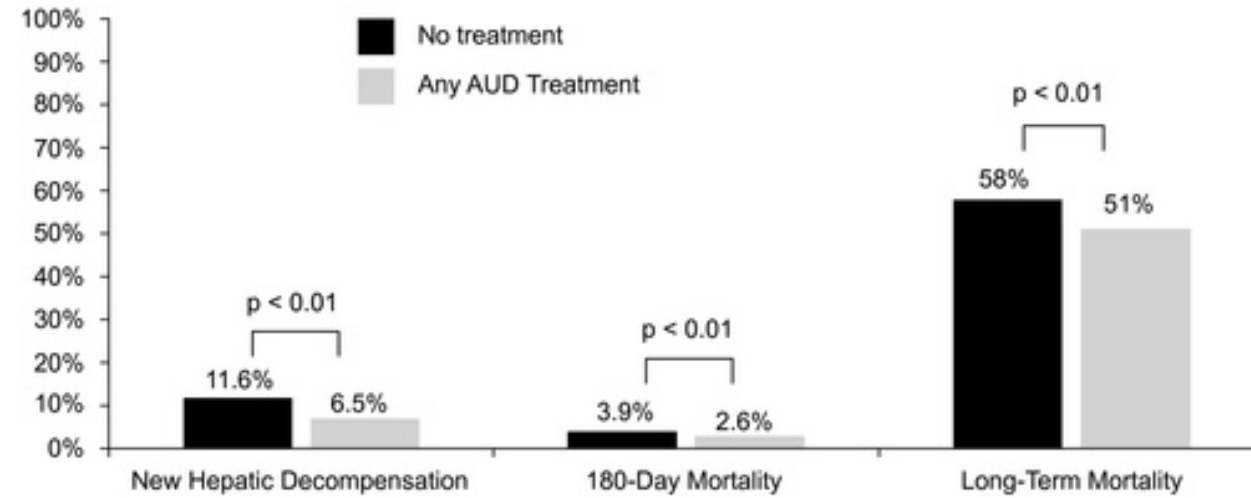
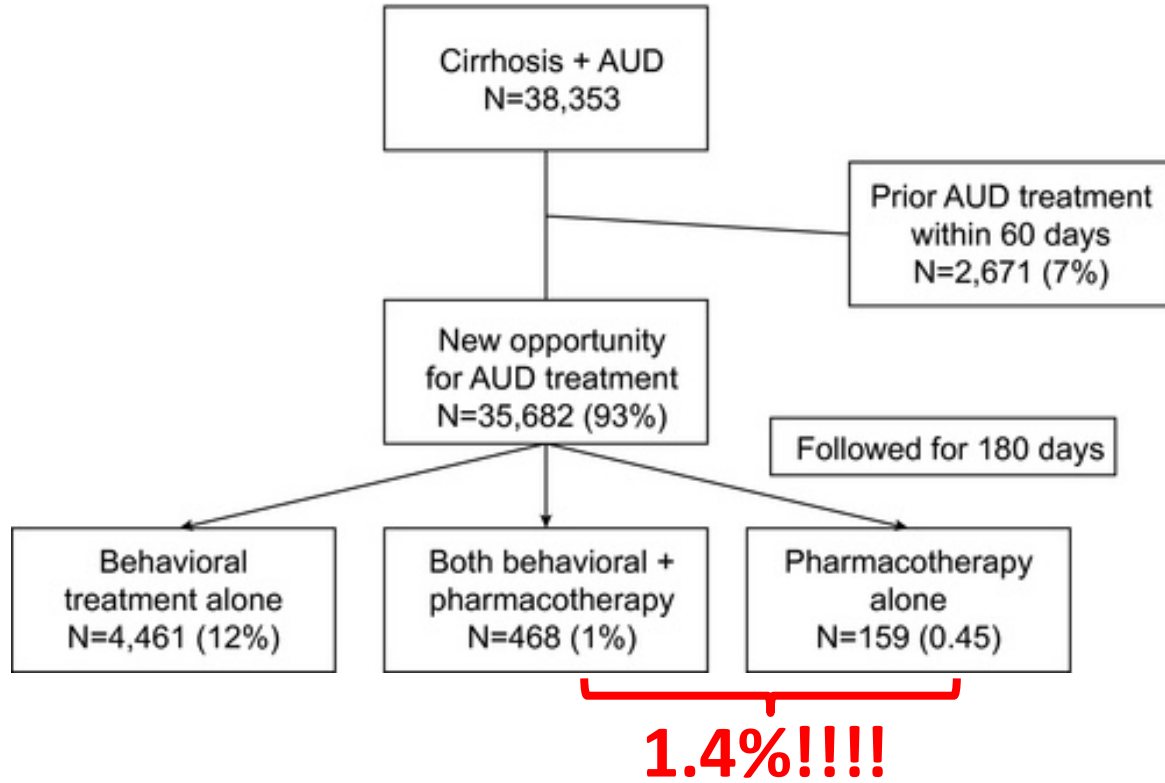
Ondansetron (1-16 mcg/kg BID)

Contraindicated medications in cirrhosis

Disulfiram



PHARMACOLOGICAL THERAPY FOR ABSTINENCE

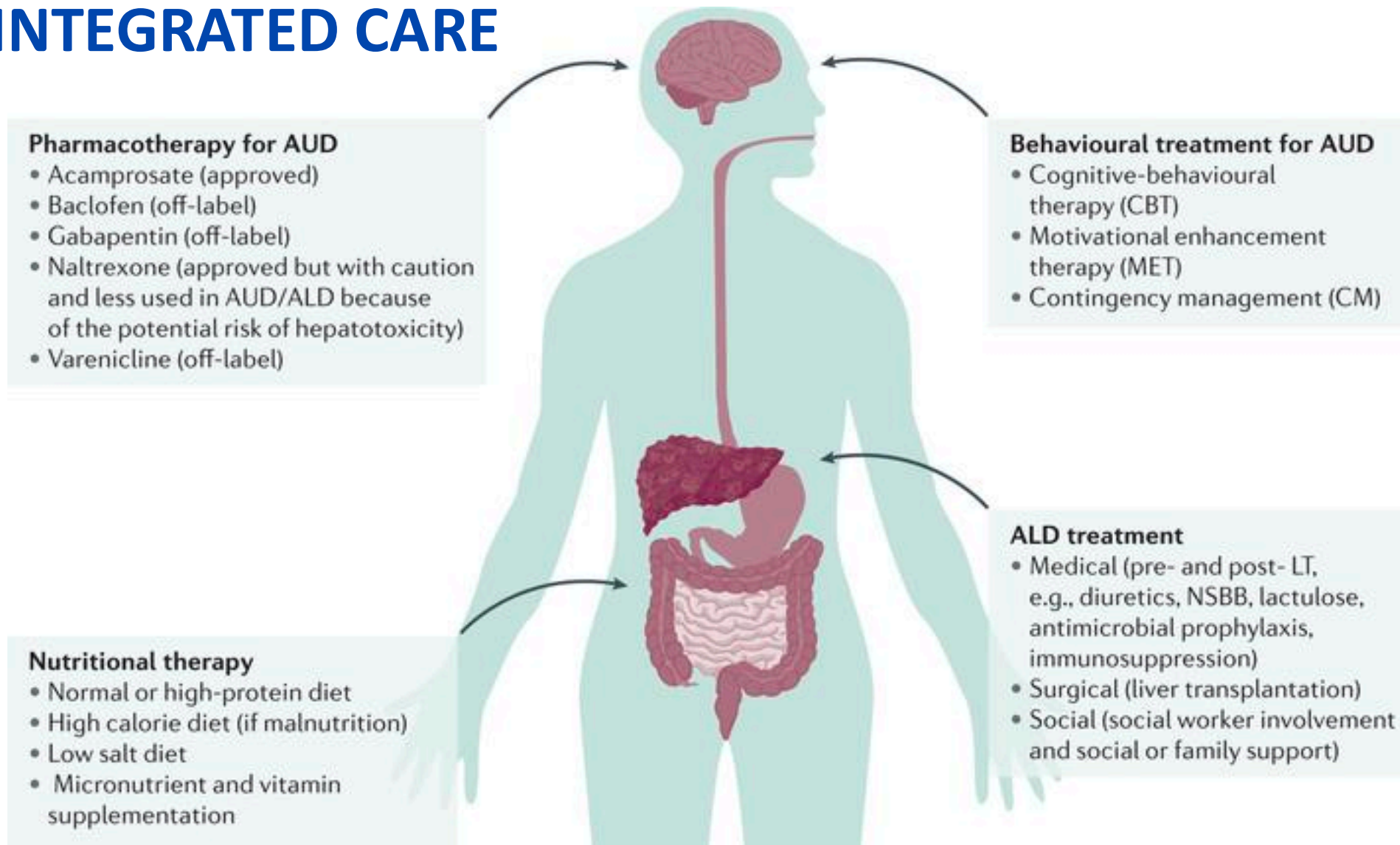


**AUD treatment
improves survival**

MAUDs have competitive NNTs

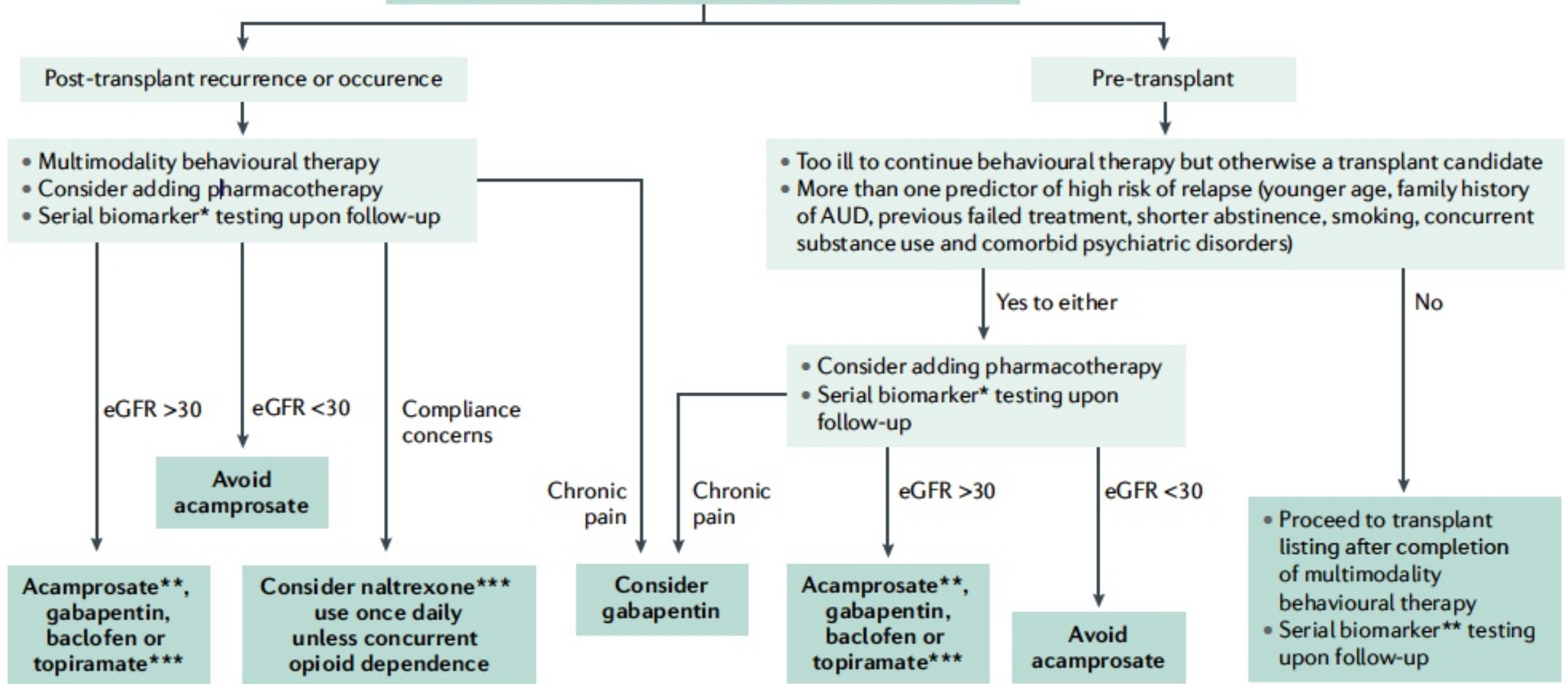
Medication	Prevention Outcome	NNT
NALTREXONE	Return to any alcohol use	20
	Return to heavy alcohol use	12
ACAMPROSATE	Return to any alcohol use	12
	Return to heavy alcohol use	--
BACLOFEN	Return to any alcohol use (within 12 wks)	2.4
Methadone (for OUD)	Continued opioid use	4
PPI (for acute PUD bleeding)	Rebleeding	15
Aspirin (for ST elevation MI)	Death	42
Aspirin (for acute ischemic stroke)	Recurrent Stroke	140

INTEGRATED CARE

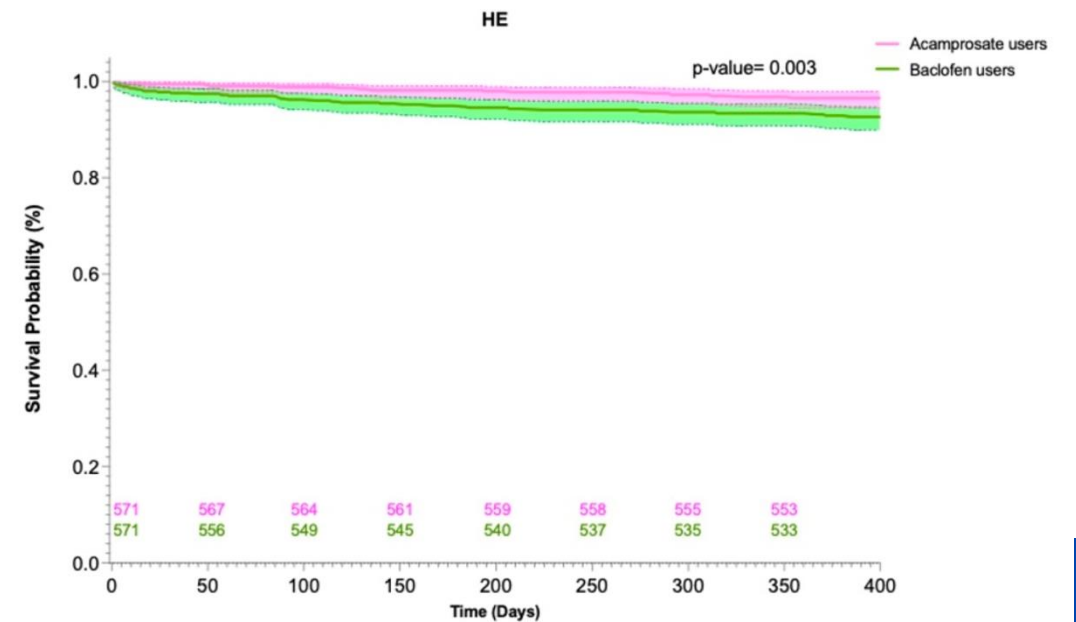
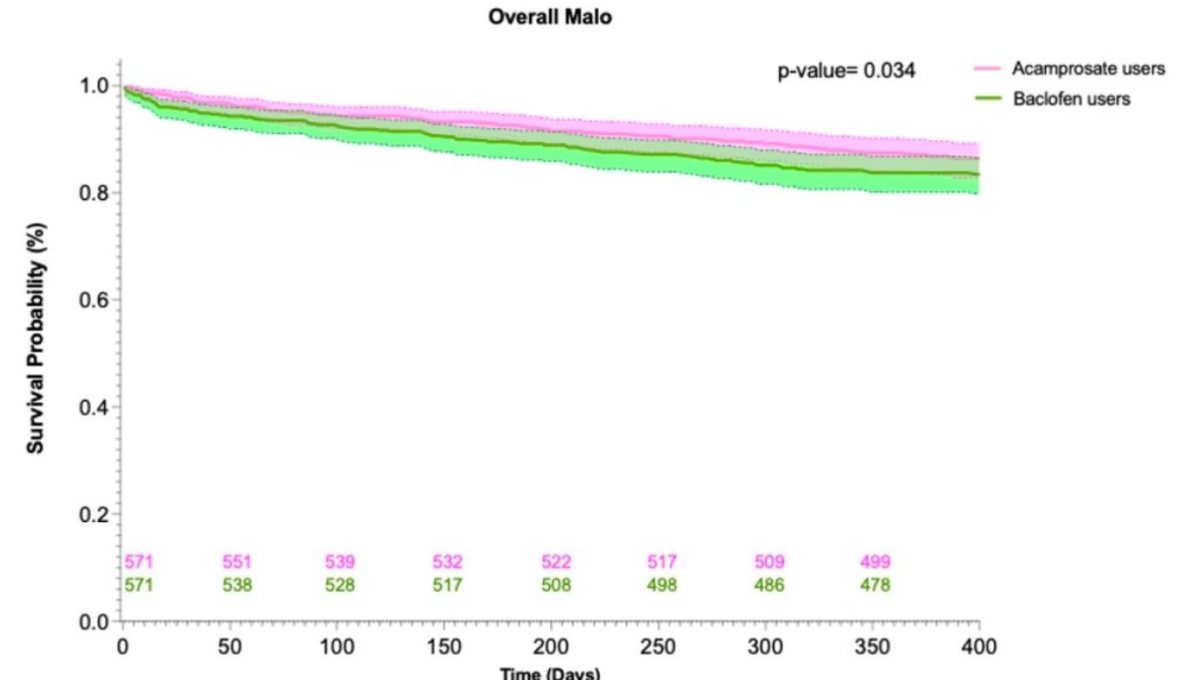
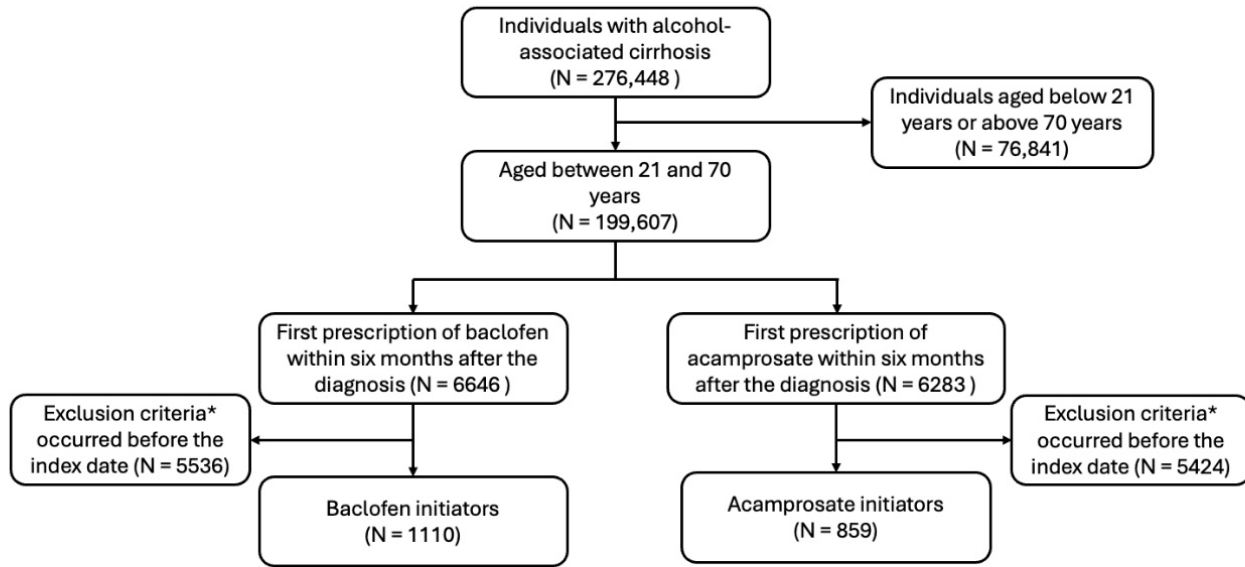


Pharmacotherapy

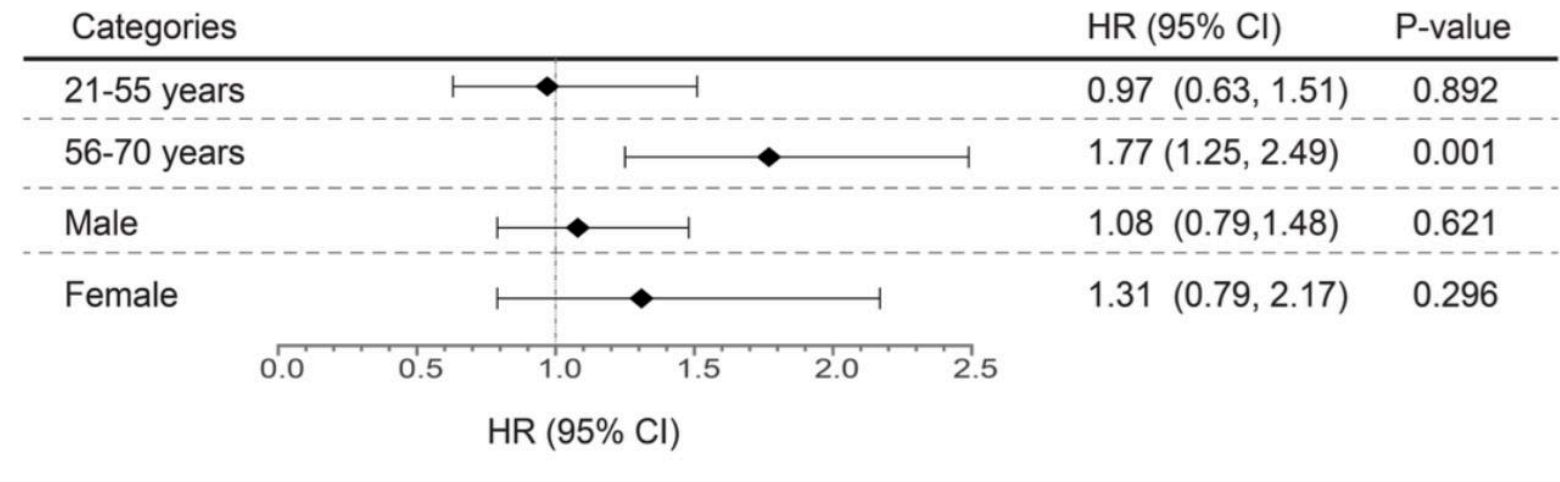
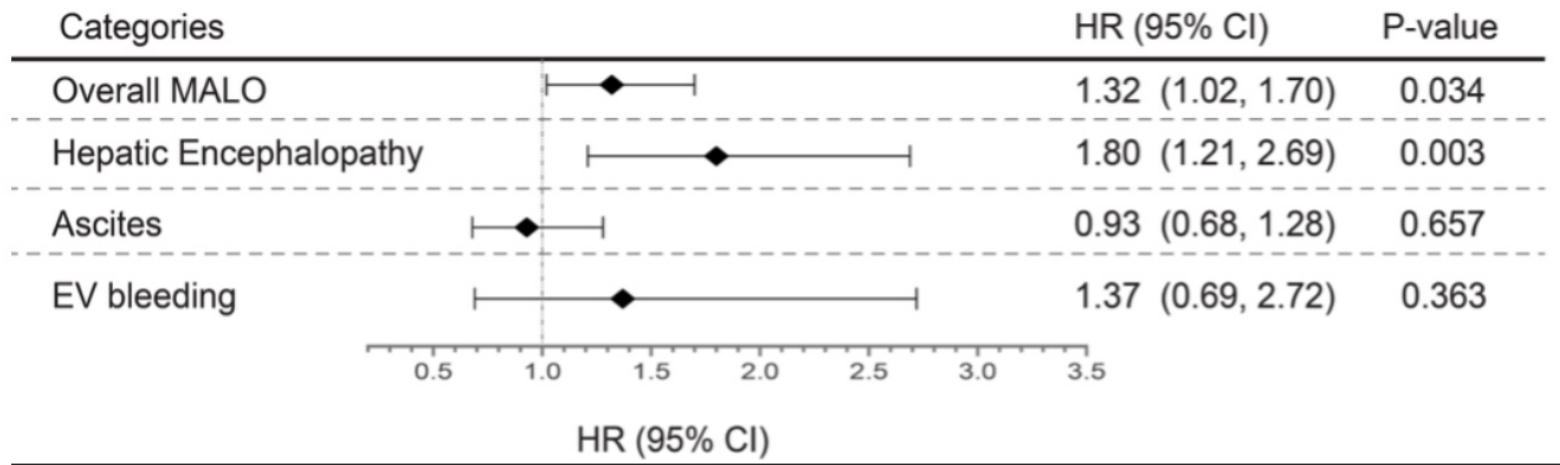
Treatment of AUD in transplant integrated care settings



Baclofen vs Acamprosate?



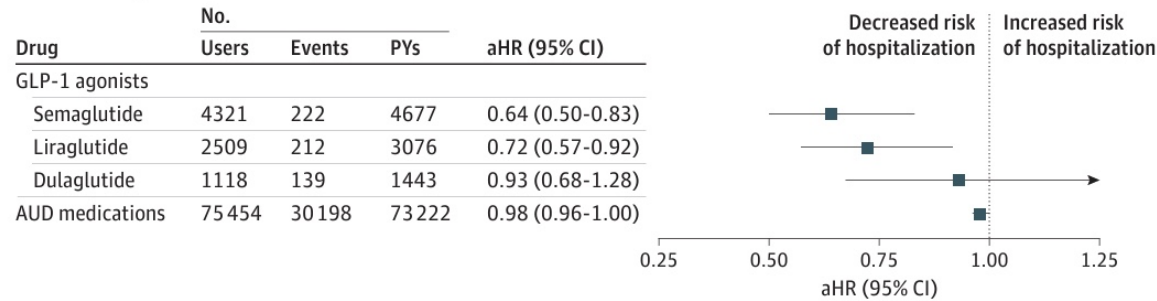
Baclofen vs Acamprosate?



GLP-1s

Figure 1. Risk of Hospitalization Due to Alcohol Use Disorder (AUD) and Substance Use Disorder (SUD)

A Risk of hospitalization due to AUD associated with use of GLP-1 agonists and AUD medications in within-individual model of persons with AUD



B Risk of hospitalization due to substance use disorder associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

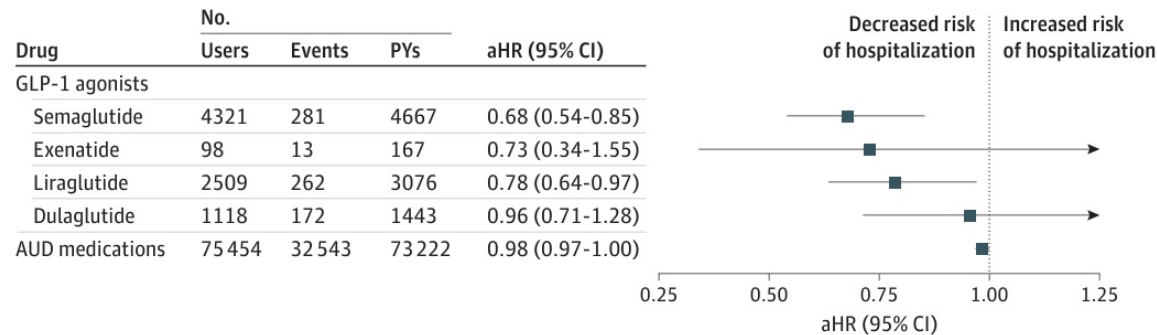
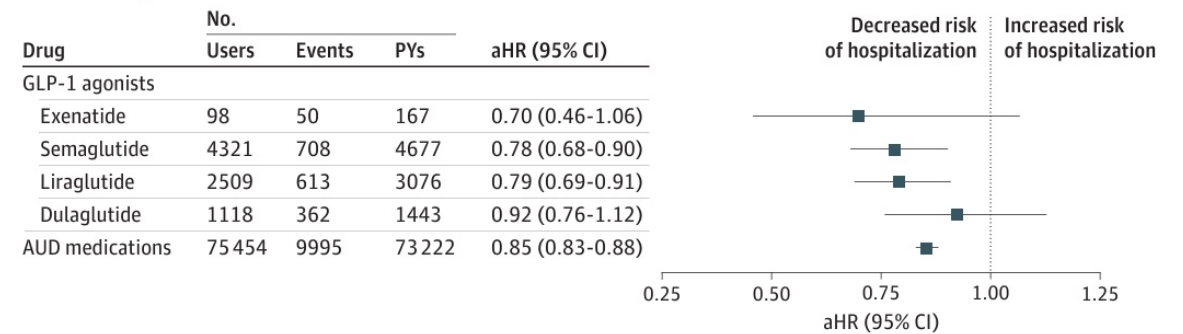
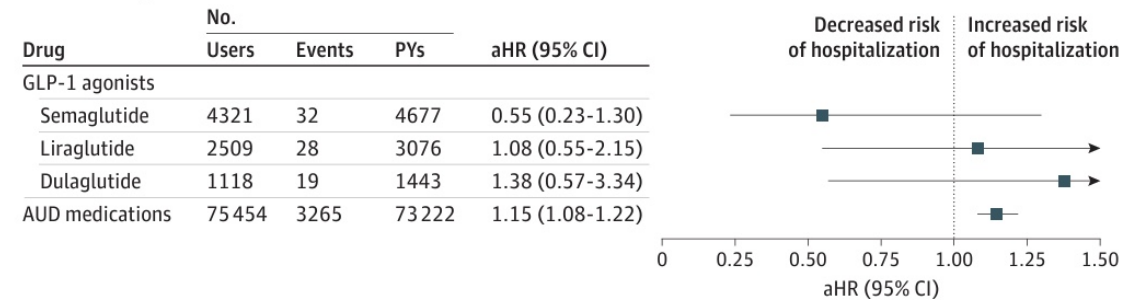


Figure 2. Risk of Hospitalization Due to Somatic Reasons and Suicide Attempt

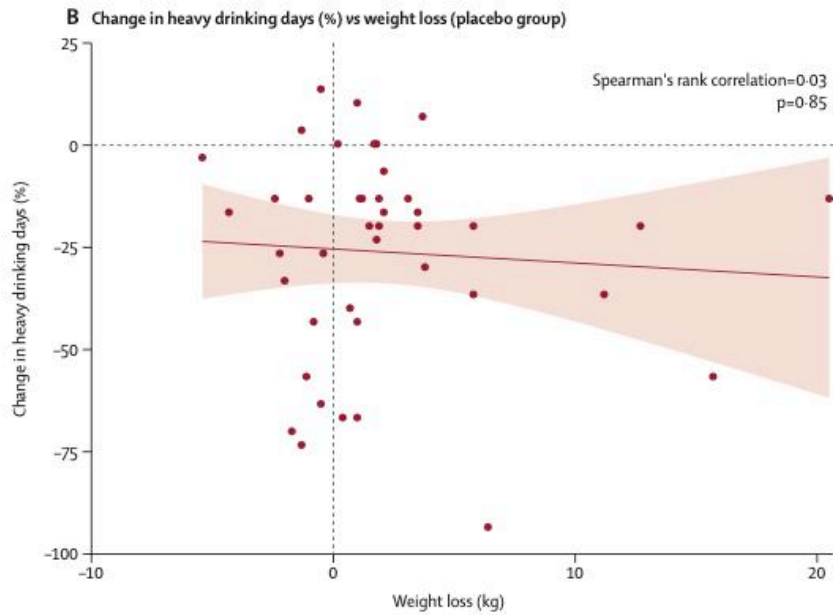
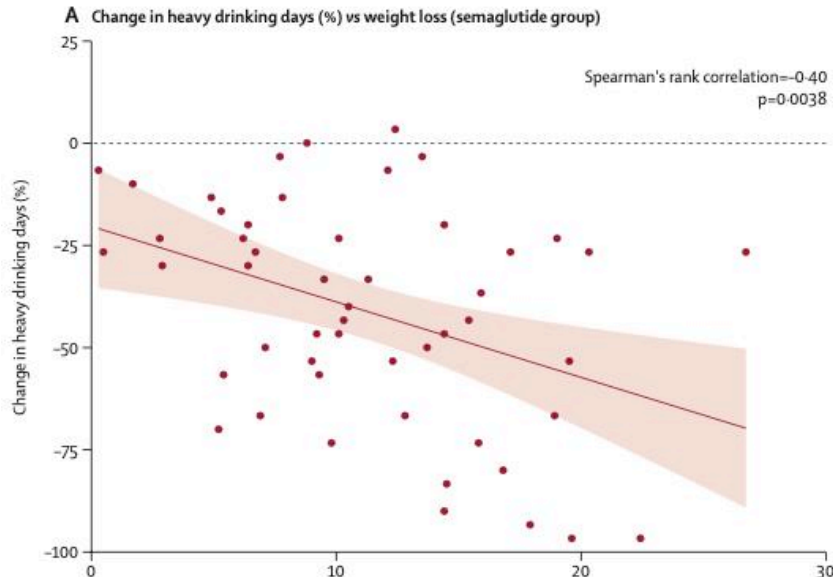
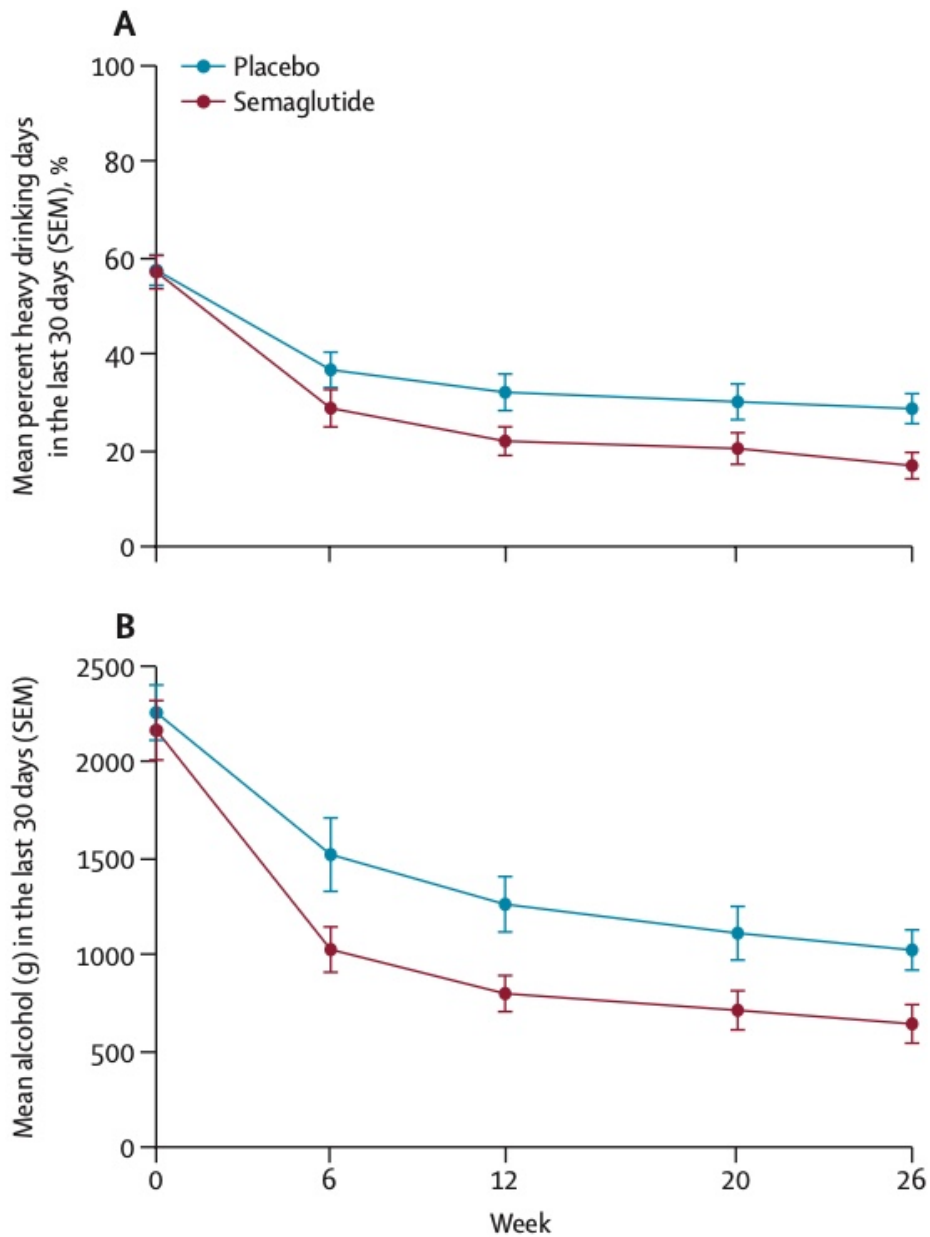
A Risk of somatic hospitalization associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD



B Risk of suicide attempt associated with use of GLP-1 agonists and medications for AUD in within-individual model of persons with AUD

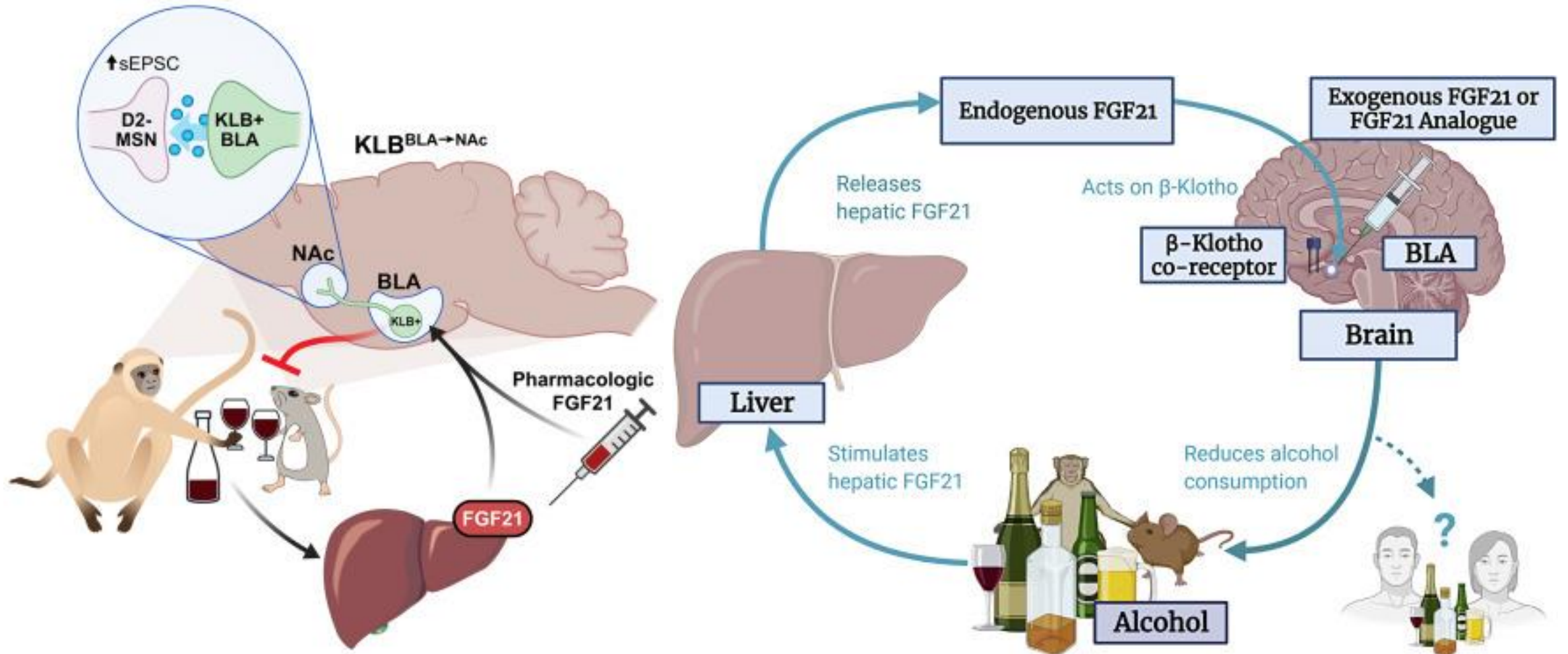


GLP-1s

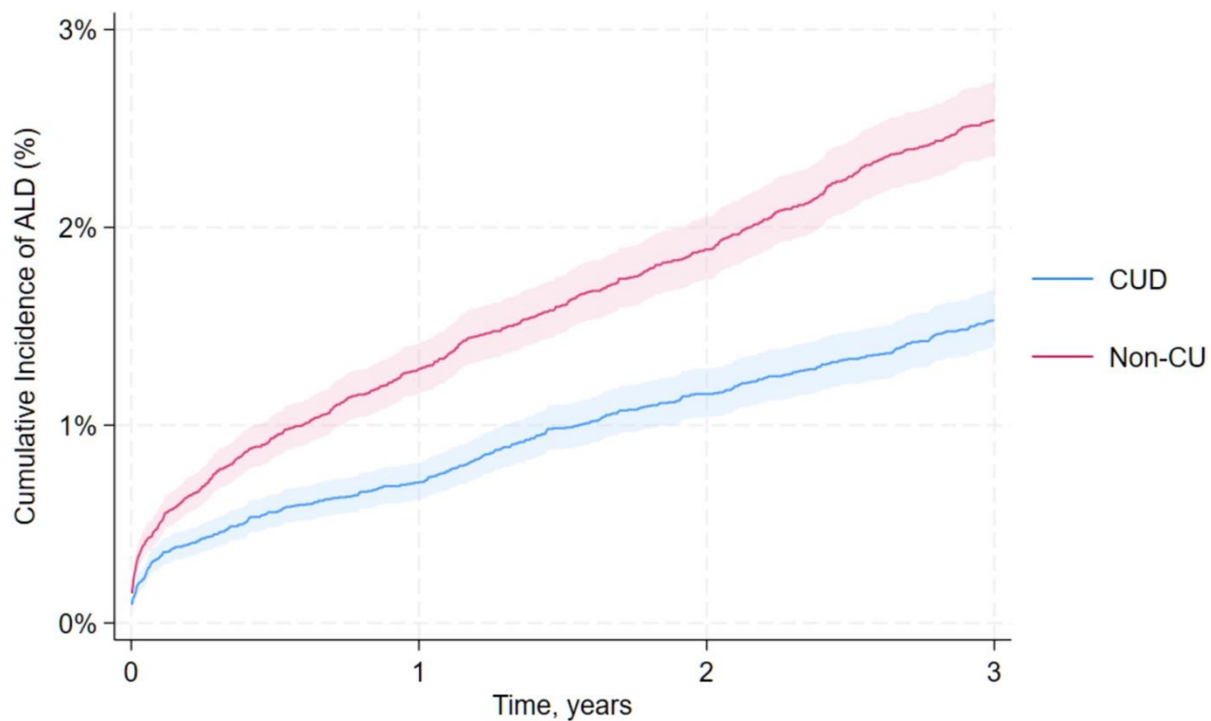


FGF21

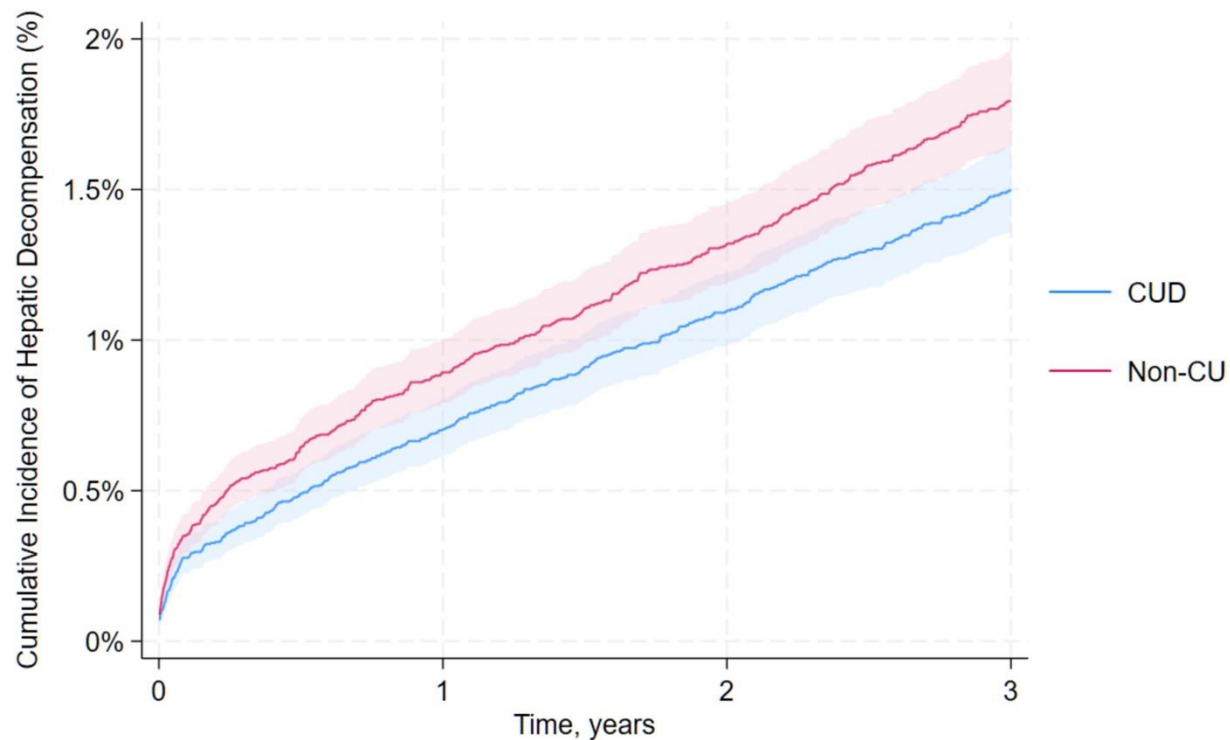
FGF21 suppresses alcohol consumption through an amygdalo-striatal circuit



Cannabinoids

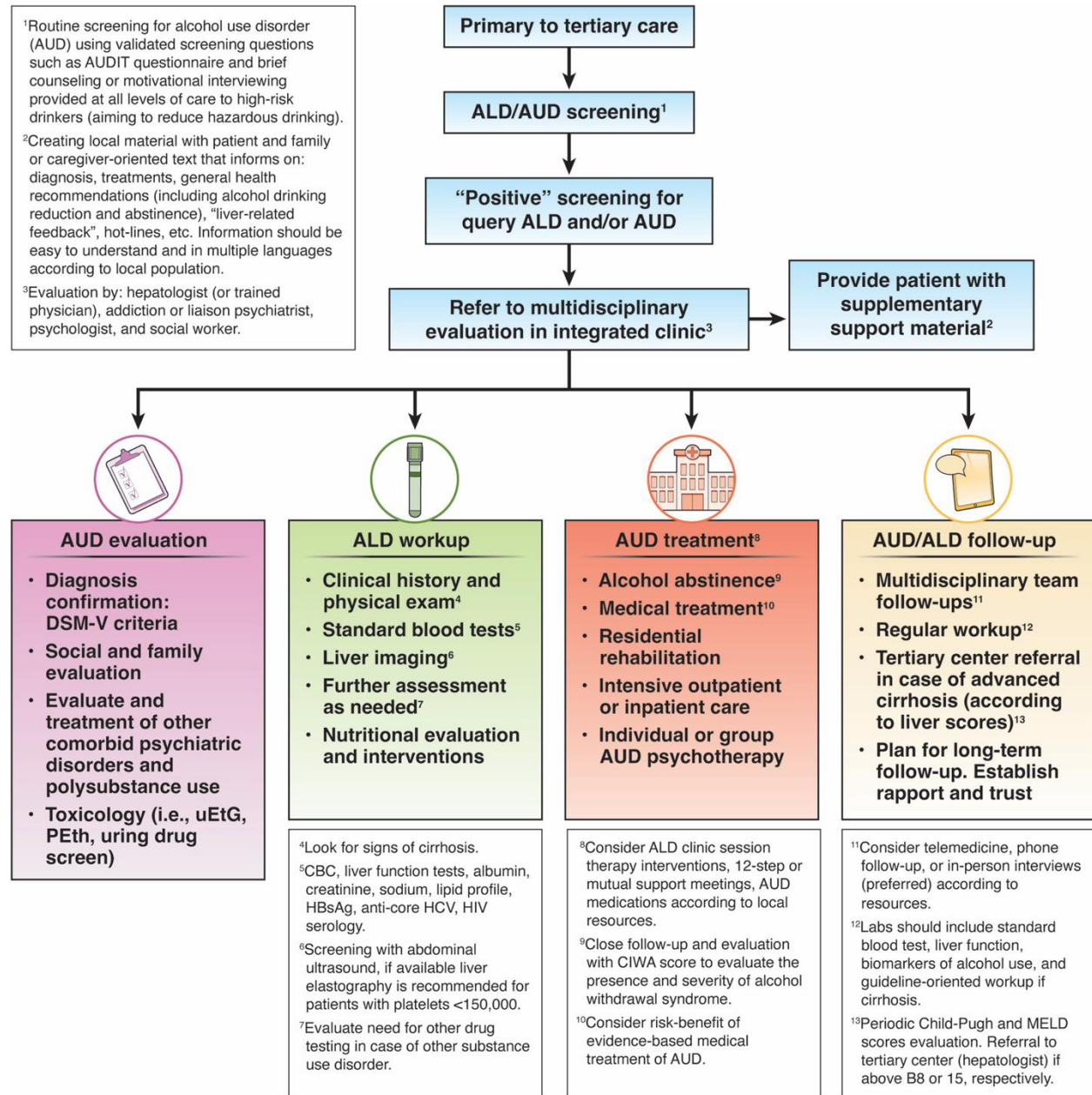
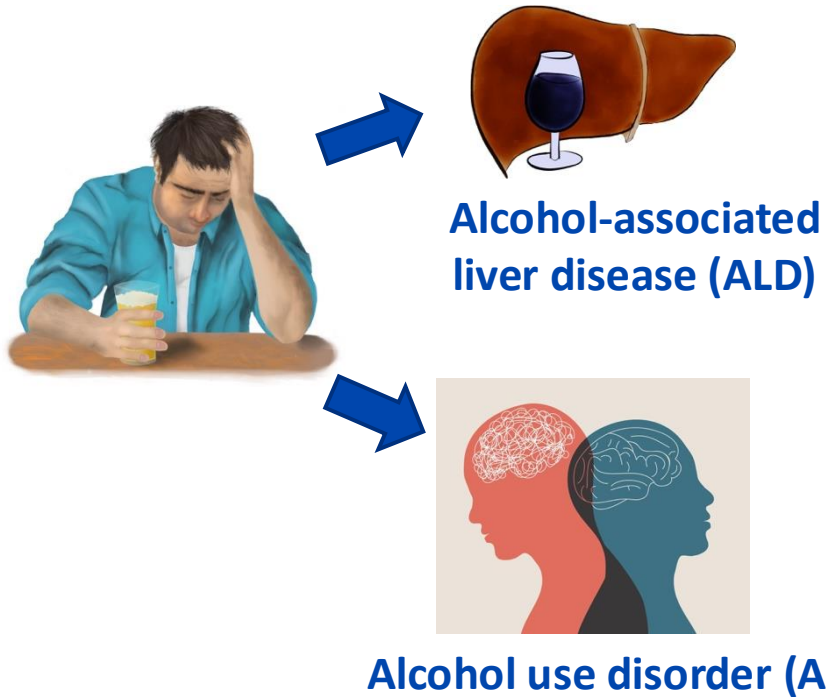


Cumulative incidence of alcohol-associated liver disease from the diagnosis of AUD

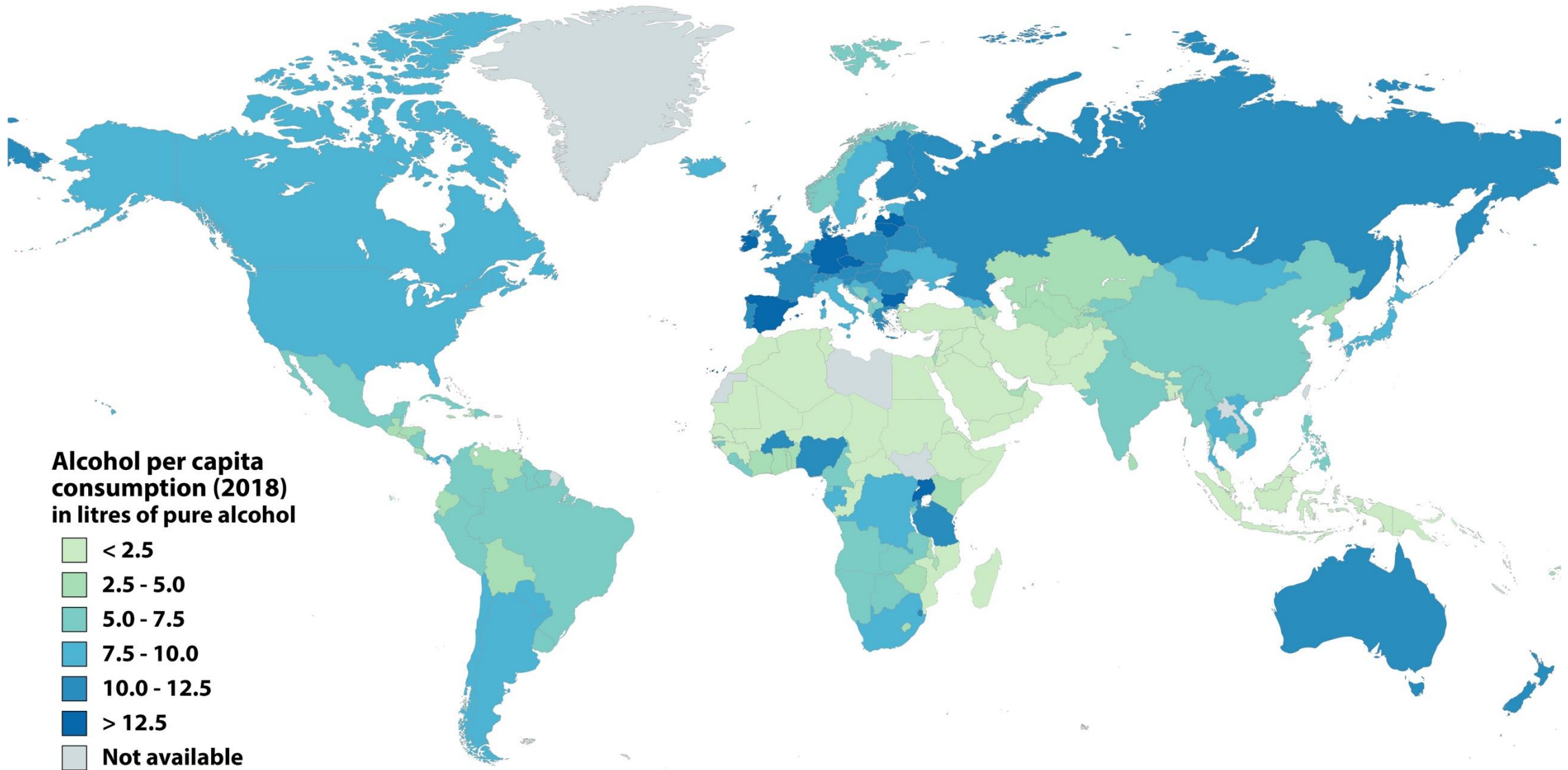


Cumulative incidence of hepatic decompensation from the diagnosis of AUD

INTEGRATED CARE



Public Health

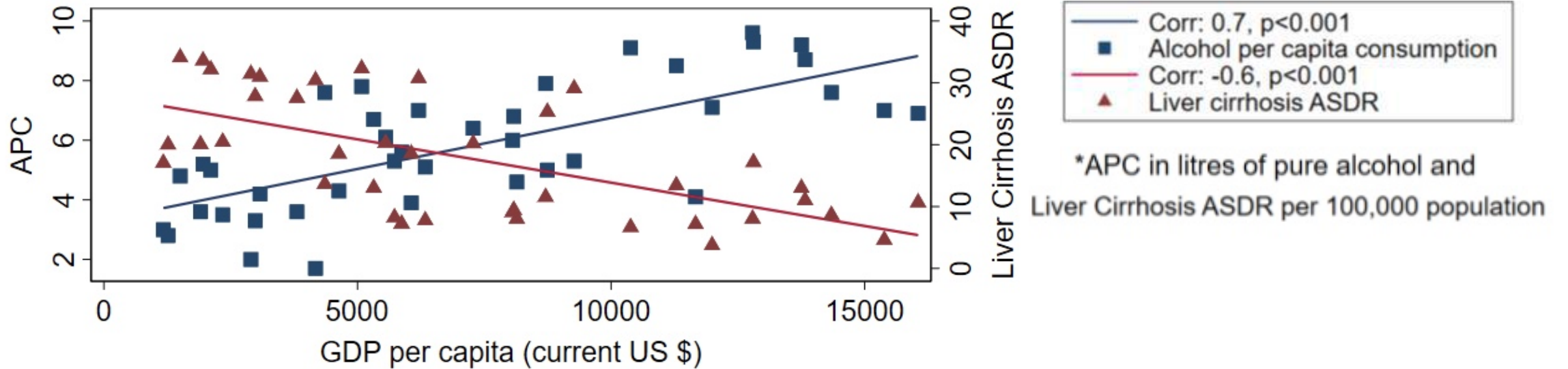


**Alcohol per capita
consumption (2018)
in litres of pure alcohol**

- < 2.5
- 2.5 - 5.0
- 5.0 - 7.5
- 7.5 - 10.0
- 10.0 - 12.5
- > 12.5
- Not available

Alcohol-Harm Paradox in Latin America

Figure 1: Relation between GDP, alcohol per capita consumption (APC) and liver cirrhosis death rates



PHP Alcohol Global: Development of a Preparedness Index

169 countries

Africa (50), America (35), Asia (33), Europe (46), Oceania (5)

Median GDP per capita: US\$ 6,146

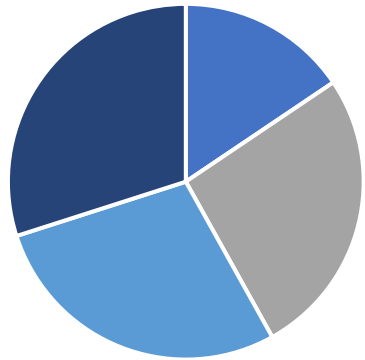
Median alcohol per capita: 6.6 liters

- Recorded: 4.7 liters
- Unrecorded 1.2 liters



Alcohol preparedness index (API) to assess public health policies on alcohol worldwide

Income level

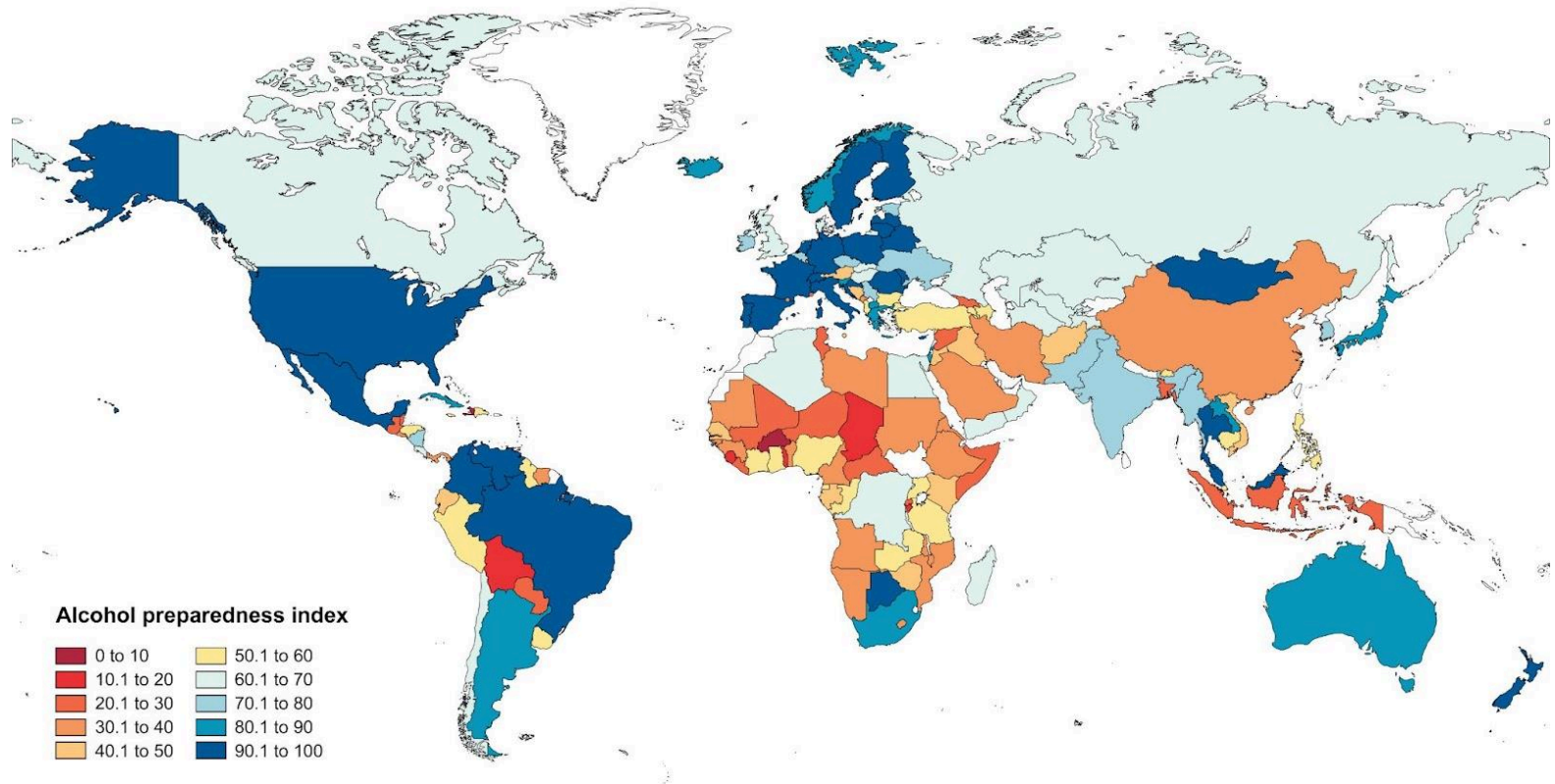


- Low
- Upper-middle
- Lower-middle
- High

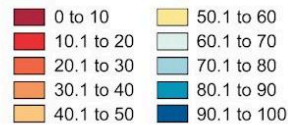
Median score
54 [34.9-76.8]

Important heterogeneity in the establishment of PHP:

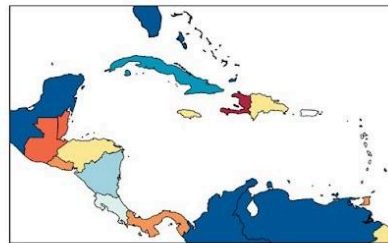
Highest: Europe
 Lowest: Africa



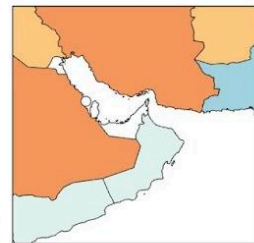
Alcohol preparedness index



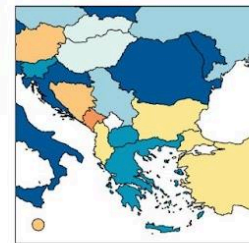
Caribbean and central America



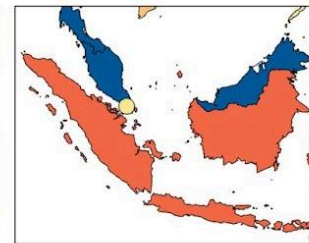
Persian Gulf



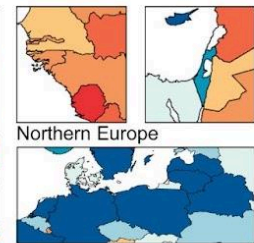
Balkan Peninsula



Southeast Asia



West Africa

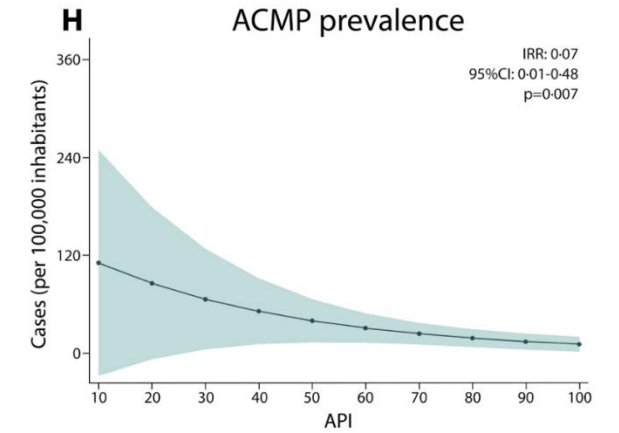
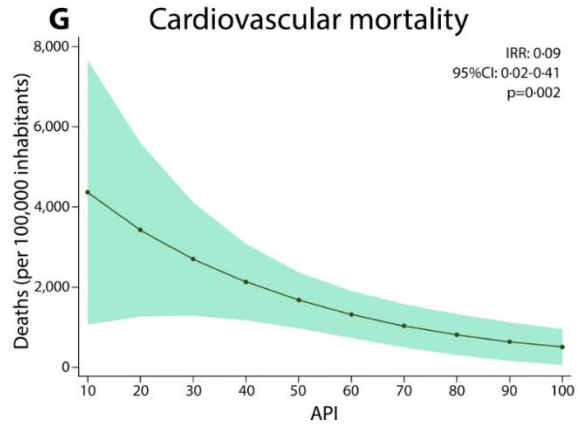
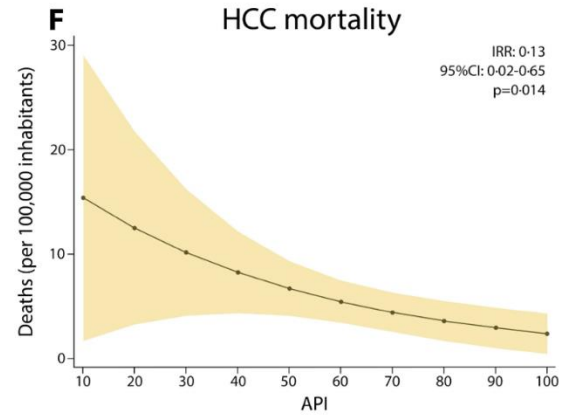
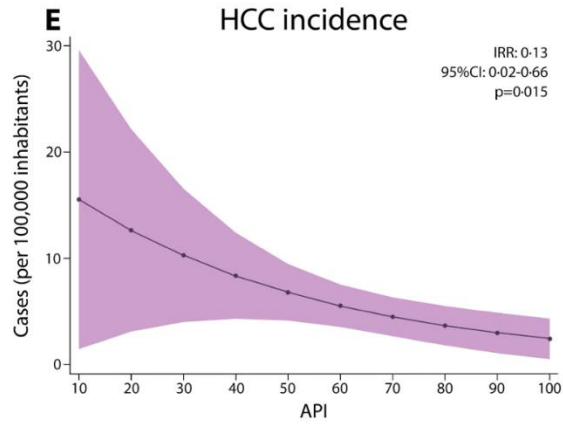
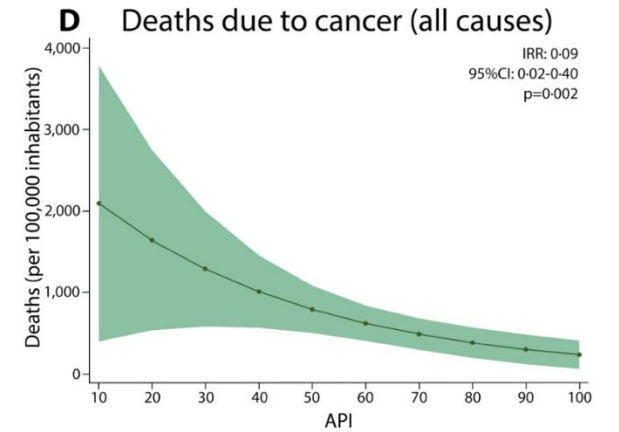
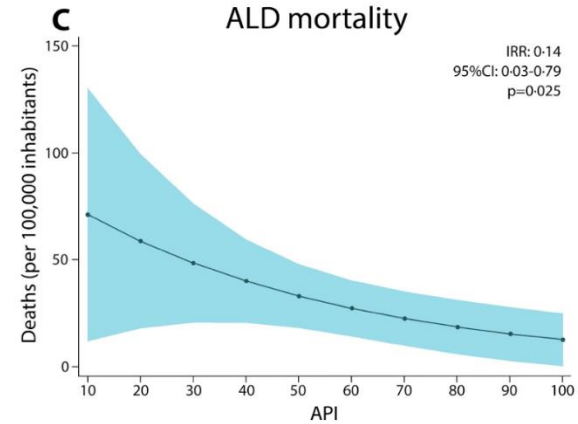
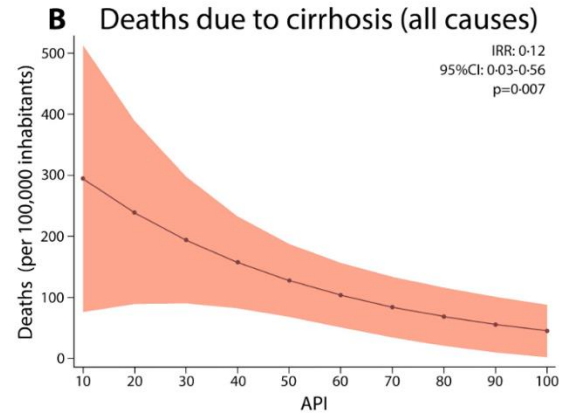
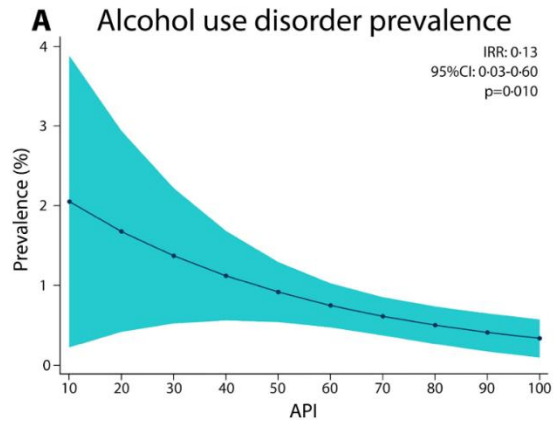


Eastern Mediterranean

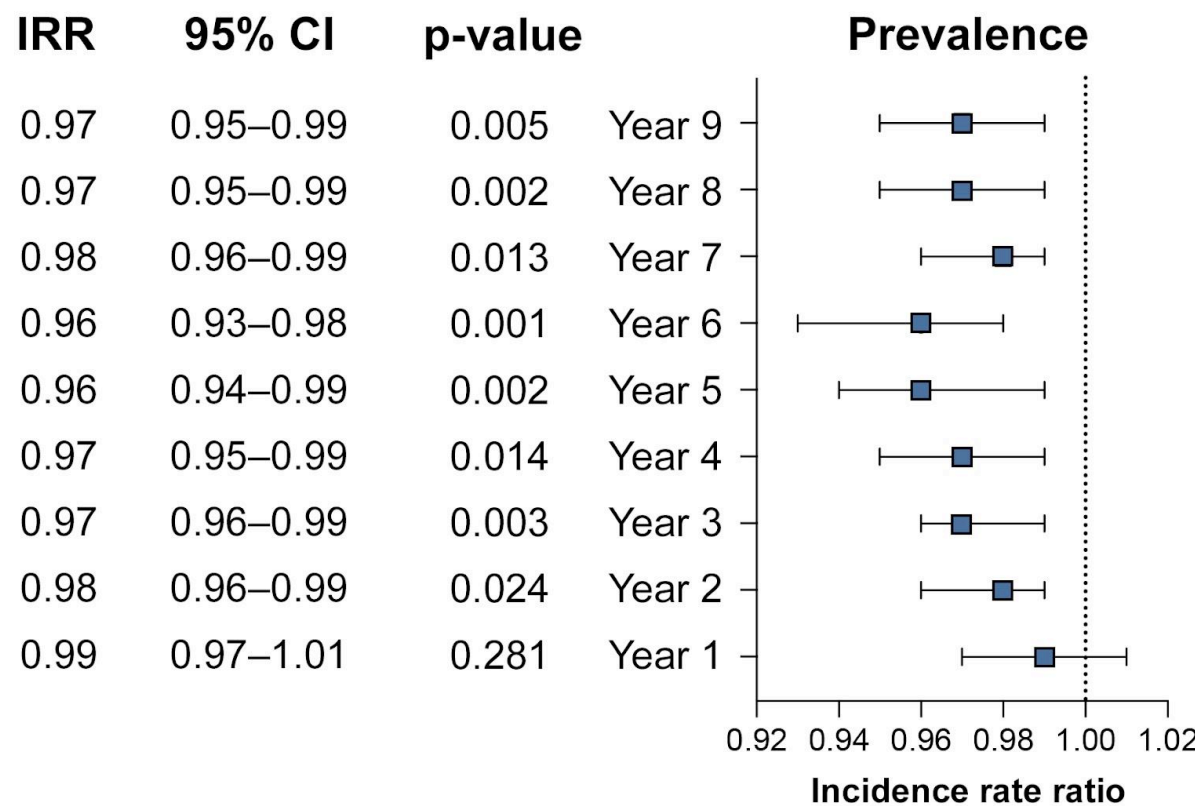


Northern Europe

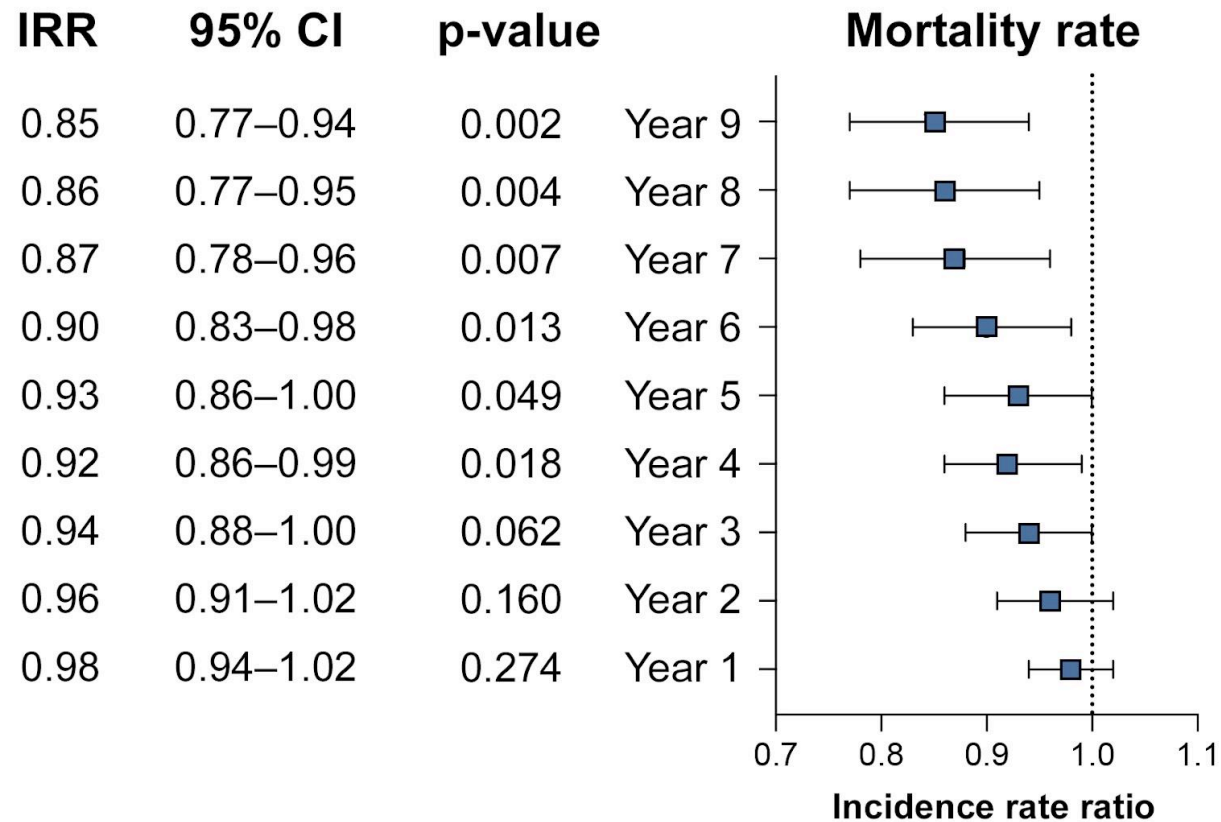




Association between alcohol-related PHP and AUD prevalence rate over time



Association between alcohol-related PHP and ALD mortality rate over time



Take Home Messages

- ALD is a leading cause for cirrhosis and LT
- AH Prognostic Assessment: MELD and Lille
- Specific pharmacological management:
 - Corticosteroids (therapeutic window), any of them
- MetALD:
 - Alcohol main driver of the disease.
 - Complex interaction between metabolic dysfunction and alcohol.
- AUD in ALD:
 - Long-term abstinence management – Integrative Care
 - MAUDs are largely safe in ALD (except for Disulfiram)
- Countries with more alcohol-related PHP have lower mortality due to ALD cirrhosis, alcohol use disorder, CV, and Cancer.



VCU School of Medicine

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UPDATES IN ALCOHOL-ASSOCIATED LIVER DISEASE

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